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REVERSIBLE CARDIAC ENLARGEMENT IN A CASE OF CONGENITAL CAVERNOUS HEMANGIOMA

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THE clinical entity known as the "reversible heart" has attracted the attention of both physiologists and clinicians for many years, although the term now used to identify it came into use only very recently. As early as 1847, Boisseau, as Matas points out,[1] described such a condition in association with arteriovenous fistula. In 1918, Zondek[2] emphasized the fact that in both myxedema and beriberi the heart might dilate and might even fail as the result of specific deficiencies, and observed that in cases of myxedema the administration of thyroid extract was followed by a return to normal cardiac dimensions. In 1925, Fahr[3] confirmed Zondek's observations on myxedema and reported a case in which a decrease of more than 6 cm. was noted in the transverse cardiac diameter after thyroid therapy. He also demonstrated that withdrawal of the thyroid extract, after the heart had returned to its normal dimensions, was followed by redilatation, and sometimes by cardiac failure.

Zondek's findings were further confirmed by Davis,[4] by Hallock[5] and by Gordon,[6] and various explanations for them were adduced. Thus, Hallock expressed the view that the cardiac enlargement associated with myxedema is the result of a hypodynamic state of the myocardium, which necessitates a compensatory dilatation for the maintenance of normal minute volume. Gordon considered that the rapid decrease in the size of the cardiac shadow after the use of thyroid extract may be due to reabsorption of the pericardial fluid.

A similar decrease in the size of the heart follows the administration of vitamin B in cases of cardiac enlargement caused by beriberi. A deficiency in vitamin B, according to Wenckebach,[7] induces physiochemical changes which cause water retention and intercellular edema.

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The microscopic changes which he demonstrated were confirmed by Weiss and Wilkins,[8] who did not, however, consider them to be of a specific character, and they were also confirmed by Keefer[9] and by Kepler.[10] All of these observers also reported the relief of cardiac symptoms and the return of the heart to normal size after the administration of vitamin B.

In 1923, Matas, in a report of 31 cases of arteriovenous aneurysm, described at considerable length the effect of this abnormality upon the size of the heart. At this time there was no unanimity of opinion upon this point. Lewis and Drury[11] believed that the cardiac enlargement resulting from arteriovenous fistula was essentially a dilatation. Holman,[12] on the other hand, proved experimentally that there was definite hypertrophy as well as dilatation; the weight of the hearts of his experimental animals was found to be increased post mortem. His idea was that the cardiac hypertrophy was due to the "increased work necessary to propel forward this increasing volume of blood flowing through" the heart. Eyster,[13-16] some years later, carried the explanation still further by postulating the injury theory, his idea being that injury to the heart muscle as the result of dilatation may be the reason for the ultimate hypertrophy.

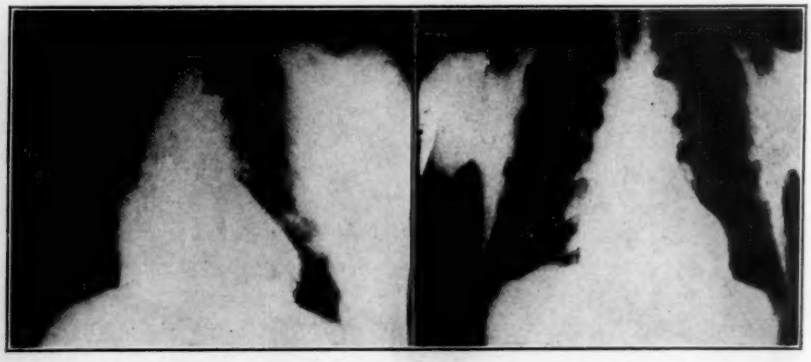

Fig. 1. Fig. 2.

Fig. 1.—R. B. Teleoroentgenogram of heart and aorta, iliofemoral arteriovenous fistula open, before compression. Longitudinal diameter of heart, 16.3 cm.; transverse diameter, 15 cm. (Matas).

Fig. 2.—R. B. Teleoroentgenogram of heart and aorta, fifty-two days after surgical suppression of the fistula. Longitudinal diameter of heart 14.8 cm.; transverse diameter, 13.3 cm. (Matas).

In 1936, Walker[17] discussed the "reversible heart" under three headings: arteriovenous aneurysm, beriberi, and myxedema. His chief contribution was to emphasize the fact that the hypertrophy is not always permanently irreversible, as was then rather generally supposed, but is frequently, if not usually, curable.

Also in 1936, Rosenblatt[18] discussed cardiac enlargement associated with chronic pulmonary tuberculosis. The enlargement may be very marked, but the institution of intensive diuretic therapy frequently results in a return to normal cardiac dimensions.

Some of the cases of arteriovenous aneurysm described by Matas in 1923 (Figs. 1 and 2) furnished the first opportunity for one of us (B. R. H.) to study the condition now known as "reversible heart." The case reported herewith was one of congenital cavernous hemangioma. Only the cardiovascular aspect is dealt with here; the surgical considerations will be presented elsewhere (R. M.).

CASE REPORT

C. C., a white man, was first seen by us in 1925, at which time he was 21 years of age. We have no very satisfactory account of his early history. At the age of 3 years, after apparently normal development up to that time, the little finger on the right hand had become discolored and later ulcerated. Some years later the same condition seems to have recurred, but no definite diagnosis was made. The patient was next heard of in 1920, at which time he registered at the Mayo Clinic because of an extensive cavernous hemangioma involving the right hand and lower forearm. After a thorough study there, the affected extremity was amputated above the involved area. A year later the condition recurred in the stump and a diagnosis of congenital subclavian arteriovenous fistula was made. Marked cardiac enlargement was reported at the same time.

Early in 1925, during the course of a routine college medical examination, the patient was told that he had an "enormous" heart, a statement which confirmed the previous report from the Mayo Clinic and apparently proved the persistence of the cardiac enlargement over the intervening four-year period. The chief symptoms at this time were dyspnea and easy fatigue.

Both of these symptoms were very marked when the patient was first seen by us in March of the same year. Dyspnea was distressing, and the mere act of undressing for the examination completely exhausted him. Physical examination revealed a tremendous conical enlargement of the stump of the right forearm (Fig. 3) due to the presence of a large, spongy hemangioma; the diameter of the stump was 17.5 cm. A loud systolic murmur was audible over the entire precordium, but was heard best over the mitral and pulmonic areas. A teleoroentgenogram showed that the heart occupied the entire thorax and was enlarged in all diameters (Fig. 4). The blood pressure was 130/80 in the left arm and 102/80 in the right arm, in which it rose to 130/80 when the hemangioma was tightly squeezed. This maneuver was associated with a marked slowing of the pulse rate (Branham's syndrome).

A month after the patient was first seen, Matas ligated the third portion of the right subclavian artery. The local hemangiomatous signs promptly disappeared but returned almost as promptly, and the patient was practically incapacitated by dyspnea. Three weeks after the first operation the right arm was disarticulated at the shoulder joint.

Improvement after the second operation was prompt and marked. Two months later the heart was apparently normal in size, the diameter having been reduced from 17.5 cm. to 13.5 cm. (Fig. 5). The murmur had completely disappeared, and from the clinical standpoint the patient seemed entirely normal.

Nothing more was heard of him until 1933, when it was reported to us by Singer, of St. Louis, that he had contracted a severe toxic pneumonia, accompanied by cardiac collapse, from which he had recovered after a very tedious convalescence. In March, 1936, the patient again consulted Singer because of a recurrence of the hemangioma at the site of the scar and in the right axilla. The heart at this time was normal in size (Fig. 6). A month later Matas removed the entire hemangiomatous mass, and the patient received several x-ray treatments. Radiographic and cardiovascular studies showed that the heart was normal in size (Fig. 7) and adequate in function.

A. *B.*

Fig. 3.—*A.* C. C., aged 19 years. Note recurrence and spread of angioma in stump of forearm (April 1, 1923).

B. C. C., aged 21 years. After ligation of subclavian vessels, with consequent temporary improvement, three weeks later (April 24, 1925) arm was disarticulated at the shoulder.

Fig. 4.—C. C. Plate taken in March, 1925, showing greatly enlarged heart.

In March, 1937, the patient again consulted us because of a recurrence of the hemangioma in the right submammary region. The heart was markedly enlarged; a teleoroentgenogram showed a transverse diameter of 15.8 cm. and a semithoracic diameter of 13.5 cm. (Fig. 8).

At this time the patient was 33 years of age and weighed 149 pounds. The pulse rate when he was at rest was 80, and the blood pressure in the left arm 140/85. The heart sounds were of good quality, there was no arrhythmia, and no murmurs were heard. The aortic second sound was louder than the pulmonic second sound, but neither was accentuated.

Because of the definite cardiac enlargement several tests of function were done. The circulation time (by the decholin method from arm to tongue) was fourteen seconds. The response to the Master two-step test was normal, and the vital capacity was 4.2 liters. Since the heart was apparently capable of efficient function, the patient was discharged after a course of roentgenotherapy. When he was last heard from, in December, 1937, he stated that he had been married for two months, and although he was working harder than he had ever worked before, because of his assumption of new obligations, he "felt better than he had ever felt in his life."

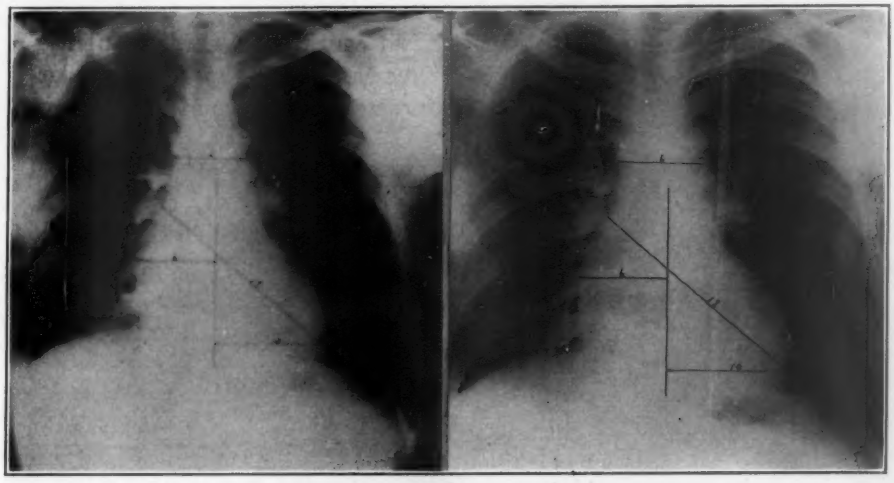

Fig. 5. Fig. 6.

Fig. 5.—C. C. View showing diminution in size of heart following ligation of subclavian vessels and disarticulation of right arm at the shoulder joint.

Fig. 6.—C. C. Plate taken eleven years after operation shows normal heart, in spite of recurrence of hemangioma at site of scar and in right axilla.

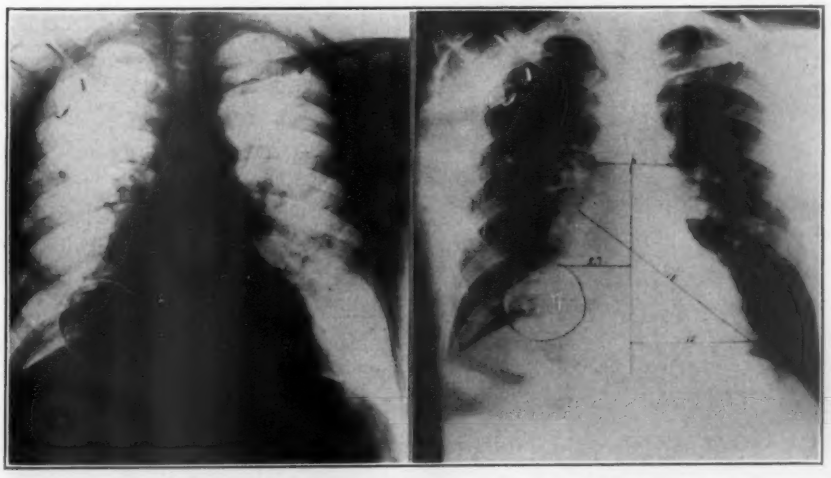

Fig. 7. Fig. 8.

Fig. 7.—C. C. Radiographic study one month after removal of hemangiomatous mass shows heart normal in size.

Fig. 8.—C. C. View taken in March, 1937, shows a markedly enlarged heart. There has been a recurrence of the hemangioma in right submammary region.

DISCUSSION

It is now generally accepted that no single factor will explain all kinds of cardiac enlargement, especially those in which there is a varying degree of reversibility. It is also believed that the cardiac enlargement which follows vitamin deficiency, for instance, differs from the enlargement associated with arteriovenous aneurysm, even though in both conditions the same basic factors might play some part in the production of the enlargement.

It is our own idea that the mechanism causing the cardiac enlargement in this case is substantially the same as the now thoroughly understood mechanism which produces the increase in the size of the heart in cases of arteriovenous fistula, as postulated by Eyster. We have no specific evidence to confirm or disprove any special theory, but we feel that in our own case there was a true mass hypertrophy of the heart, as well as an initial dilatation. It does not seem plausible that cardiac dilatation without hypertrophy could exist over as long a period of time as it did in this case without the occurrence of heart failure. It is not necessary to commit oneself to a special theory, however, to comprehend what apparently happened in this case. Radiographic evidence showed that a heart which had been dilated and hypertrophied for at least six years returned to approximately normal size and functioned efficiently. Twelve years later the cardiac dilatation and hypertrophy recurred, yet the heart, by standard adequacy tests, was shown to be capable of carrying on its physiologic function in an apparently normal manner.

SUMMARY

1. Congenital hemangioma of the upper extremity has been added to the group of diseases which produce the condition known as "reversible heart."

2. In the case reported, definite cardiac enlargement had persisted for four years prior to amputation of the right arm and forearm for a cavernous hemangioma; after operation the cardiac dimensions returned to normal size. Twelve years later the heart again became enlarged, following a metastasis or activation of hemangiomatous "nests" in the right submammary region. Adequacy tests, however, revealed cardiac competency.

3. The mechanism of the cardiac enlargement in this case is discussed, and the injury theory of Eyster is accepted as the underlying cause of the hypertrophy, just as it is the most reasonable explanation for the reversible cardiac enlargement associated with arteriovenous fistula.

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CALCAREOUS DISEASE OF THE AORTIC VALVE

A Study of Two Hundred Twenty-Eight Cases*

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CALCAREOUS disease of the aortic valve was regarded for many years as somewhat of a pathologic curiosity. Since its original description by Mönckeberg,[1] in 1904, there has been much speculation regarding its etiology. Such speculation has found expression, for the most part, in hypotheses postulating either an atherosclerotic[2-5] or an inflammatory origin.[6-9] Regarding the latter, both rheumatic and nonrheumatic infections have been incriminated, and the intriguing but unsupported supposition that calcareous disease of the aortic valve represents the healed stage of subacute bacterial endocarditis has been entertained.

There are several important reasons why the earlier investigations of isolated examples or of small groups of cases yielded information which placed calcareous disease of the aortic valve in a category somewhat out of relationship with the conventional and well-recognized forms of cardiac disease. Those reasons were the belief that calcareous disease of the aortic valve was rare, that its distribution as regards sex was peculiar, that its clinical behavior differed in many respects from that of the better known forms of inflammatory heart disease, and, finally, that diagnostic criteria had not been recognized by the clinician until relatively recent years. That a disease characterized by rather dramatic physical signs should have escaped attention even through that phase of the history of diagnosis in which particular heed was paid to cardiac murmurs is quite surprising. Perhaps the one factor which has served as the main stimulus in reviving interest in calcareous disease of the aortic valve has been the development of a fluoroscopic procedure whereby calcified aortic leaflets can be visualized during life (Fig. 1).[10-14] Occasionally, deposition of calcium is sufficiently extensive to permit its demonstration on the roentgenogram (Fig. 1). In this connection it is interesting to note that Christian,[6] impressed by the marked degree of calcification found in the group of cases which he reported in 1931, predicted the feasibility of demonstrating these calcified leaflets by roentgenologic examination.

Since the review of our material was begun, Clawson, Noble, and Lufkin[15] have published an analysis of 200 cases of calcified aortic valve studied at necropsy. They noted, as have previous writers, its preponderance among males and its high incidence in the older age groups. With

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due emphasis on the pathologic features and possible etiologic factors, their studies indicate that a "history of rheumatism" and stigmas of previous rheumatic infection (namely, deformities of the mitral or other valves, adherent pericardium, presence of Aschoff nodules in the myocardium, microscopic evidence of proliferative inflammation, and presence of blood vessels in the cusps and rings) occurred with almost the same frequency in calcareous disease of the aortic valve as in other healed rheumatic deformities of the valve.

Fig. 1.—Calcareous disease of the aortic valve in which calcification was sufficiently extensive to be demonstrable roentgenographically. This condition usually is demonstrable fluoroscopically only.

In order to avoid confusion, we wish to describe very briefly the essential criteria which have been defined as diagnostic of calcareous stenosis of the aortic valve.[6] A loud, rough systolic bruit is present over the base of the heart and is conducted into the vessels of the neck and, in many instances, over the entire precordium. The second heart tone is absent or diminished in intensity and, in those cases in which there is an

associated aortic regurgitation, it is replaced by a soft blowing diastolic murmur. A thrill is usually palpable over the upper part of the sternal region. Evidence of cardiac hypertrophy usually can be elicited, and roentgenologic examination reveals the presence of deposits of calcium within the aortic cusps or annulus.

MATERIAL FOR STUDY

In the present study the material at our disposal was arranged in groups for reasons that will become evident. Group 1 consisted of 106 cases of calcareous disease of the aortic valve with data obtained clinically and at necropsy. Group 2 consisted of ninety cases in which all the criteria necessary to permit a clinical diagnosis of calcareous stenosis of the aortic valve were satisfied, and calcification in the leaflets of the valve or in the annulus was demonstrated fluoroscopically. This group represents cases observed in the years 1933 to 1937, inclusive, and is distributed as follows: 1933, four cases; 1934, fourteen cases; 1935, seventeen cases; 1936, thirty-three cases; 1937 (part) twenty-two cases. Group 3 consisted of thirty-two cases of roentgenologically demonstrable calcification of the aortic leaflets, in which, according to the concepts laid down in the earlier literature, not all of the criteria necessary to permit a clinical diagnosis of calcareous stenosis of the aortic valve were satisfied. The main differences between group 3 and group 2 consist of preservation of the second aortic sound in the cases of group 3, which we regarded as indicative of dynamic function of the leaflets, the less constant occurrence of a basal thrill in the cases of group 3, less evidence clinically of cardiac hypertrophy, and, on the whole, fewer cardiac symptoms in the cases of group 3. Because of these differences, these cases, when encountered clinically, were catalogued separately as "calcified aortic valves." But in the light of information subsequently disclosed in the clinicopathologic survey of cases of calcareous disease of the aortic valve in which necropsy was performed, we feel satisfied that these cases should be classified with the second group, and that they represent, as we will show presently, definite but milder degrees of stenosis of the aortic valve (graded 1 and 2 on the basis of 1 to 4) with lesser degrees of calcification of the aortic leaflets; for the sake of clarity, they will be considered separately for the time being.

Controls.—A survey was made of 2,616 consecutive necropsies performed during the period 1933 to 1937, inclusive, to ascertain the incidence of calcareous disease of the aortic valve among all varieties of healed rheumatic valvular disease. There were 127 instances (4.8 per cent of all necropsies) in which some variety of healed valvular defect was found. Of these, twenty-three (18.1 per cent) were found to be calcareous disease of the aortic valve (0.9 per cent of all necropsies).

Review was made of 106 cases of mitral stenosis in the general material obtained at necropsy with reference to history of rheumatic fever, associated valvular involvement, and adherent pericarditis. In 63 per cent

of cases a history of rheumatic fever had been obtained; associated valvular disease was found in 63 per cent, and there was evidence of healed rheumatic pericarditis in 23 per cent.

PATHOLOGIC DATA

Degrees of Stenosis and Calcification of the Aortic Valve.—It was apparent immediately that the degree of stenosis of the aortic valve varied considerably. In eighteen cases the degree of stenosis was extreme (grade 4). In many of these the degree of fusion and calcification of the cusps had reduced the aortic opening to a mere slit (6 to 7 mm. by 2 to 3 mm.) and, in one case, there was complete fusion of all the cusps, a fenestration through one cusp affording the only opening from the left ventricle into the aorta. In forty cases stenosis was marked (grade 3). In forty-five cases stenosis was considered moderate in degree (grade 2). The degree of fusion of the cusps was less marked than in the previous group but, at the same time, the orifice of the aortic valve was diminished definitely in size. Finally, there were three cases in which stenosis was minimal (grade 1), but there was unmistakable evidence of calcification, most marked in the region of the aortic ring.

In order to illustrate clearly the picture of calcareous disease of the aortic valve with minimal stenosis, complete details relative to one of these three cases are presented. A man, aged 68 years at the time of his death in 1937, was first seen at the Mayo Clinic in 1920. In the seventeen years that followed he was examined on many occasions by one of us (F. A. W.). At his first visit it was noted that there was a soft systolic murmur audible at the aortic and mitral areas. He had no cardiac complaints and his blood pressure was 140/74. Four years later he returned and gave a history of short attacks of paroxysmal tachycardia and complained of heart consciousness. The objective manifestations were essentially the same as on previous visits except that the bruit was described as being definitely aortic in situation, and accentuation of the second aortic sound was noted. There was no evidence of diminished tolerance for exercise, and the electrocardiographic examination gave evidence of a rate of 107, sinus tachycardia, and left ventricular preponderance. Several visits in the succeeding nine years disclosed no new features; the only cardiac complaints noted were relative to the patient's consciousness of extrasystoles. The aortic systolic bruit was attributed to aortic sclerosis. In 1935 he returned for a general examination. Apart from palpitation, new cardiac symptoms had not developed, and the physical findings corresponded with those of previous visits. The second aortic sound again was described as distinct and accentuated. On this occasion fluoroscopic examination of the aortic valve was carried out and this revealed calcification of the aortic leaflets. Electrocardiographic examination gave evidence of a rate of 73, sinus rhythm, left ventricular preponderance, and delayed A-V conduction (the P-R interval measured

0.28 second). After the administration of $\frac{1}{100}$ grain (0.0006 gm.) of atropine sulfate subcutaneously, however, the A-V conduction time measured 0.20 second, indicating that the conductive defect previously noted was not caused by organic cardiac disease. The patient's blood pressure was 160/84, and examination of the ocular fundi revealed slight sclerosis of the retinal arteries.

The patient returned in 1937 because of rapid decline in general health, and succumbed to widespread metastasis to bone from sarcoma of the mesentery. Throughout his entire history there was neither significant evidence of limitation of cardiac reserve nor evidence clinically or roentgenologically of much cardiac hypertrophy. At no time was a thrill elicited. At necropsy the heart weighed 420 gm. The aortic leaflets showed definite calcification macroscopically, but not to the extent of rendering the cusp as rigid as in the more advanced degrees of calcification. There was only slight fusion of the margins of the cusps. The coronary arteries, as well as the aorta, were extremely arteriosclerotic, in marked contrast with most of the cases in which there were higher degrees of stenosis of the aortic valve. In summary, this case is an example of comparatively minimal calcareous disease of the aortic valve, with minimal stenosis, presenting physical signs which do not satisfy, for very obvious reasons, all the criteria previously described as diagnostic of calcareous stenosis of the aortic valve. By the same token, the mechanical disadvantage imposed on the left ventricle by the presence of such stenosis is not great enough to result in marked cardiac hypertrophy or in appreciable limitation of cardiac reserve. We wish to emphasize, further, that this lesion was present seventeen years before death and, unquestionably, had its inception many years before the patient first came under our observation.

The degree of calcification, in the majority of cases, paralleled the degree of stenosis (Fig. 2). In some cases, there was an extension of calcification to the ventricular wall, involving secondarily the aortic cusp of the mitral valve and, in three instances, there was extension into the base of the aorta in such a way as to obstruct the orifices of one or both coronary arteries. Interestingly enough, all three patients died suddenly. At times, calcification was disposed in the form of irregular cauliflower-like masses or nodules, suggesting that the calcifying process had effected a stony metamorphosis in a previously inflammatory vegetation, an appearance which, no doubt, suggested the possibility to some investigators that the disease represents the healed stage of subacute bacterial endocarditis.

STIGMAS OF PREVIOUS RHEUMATIC INFECTION (CASES IN WHICH NECROPSY WAS PERFORMED)

History of Rheumatic Fever.—Single or repeated attacks of acute rheumatic fever were recorded in sixteen of the 106 cases.

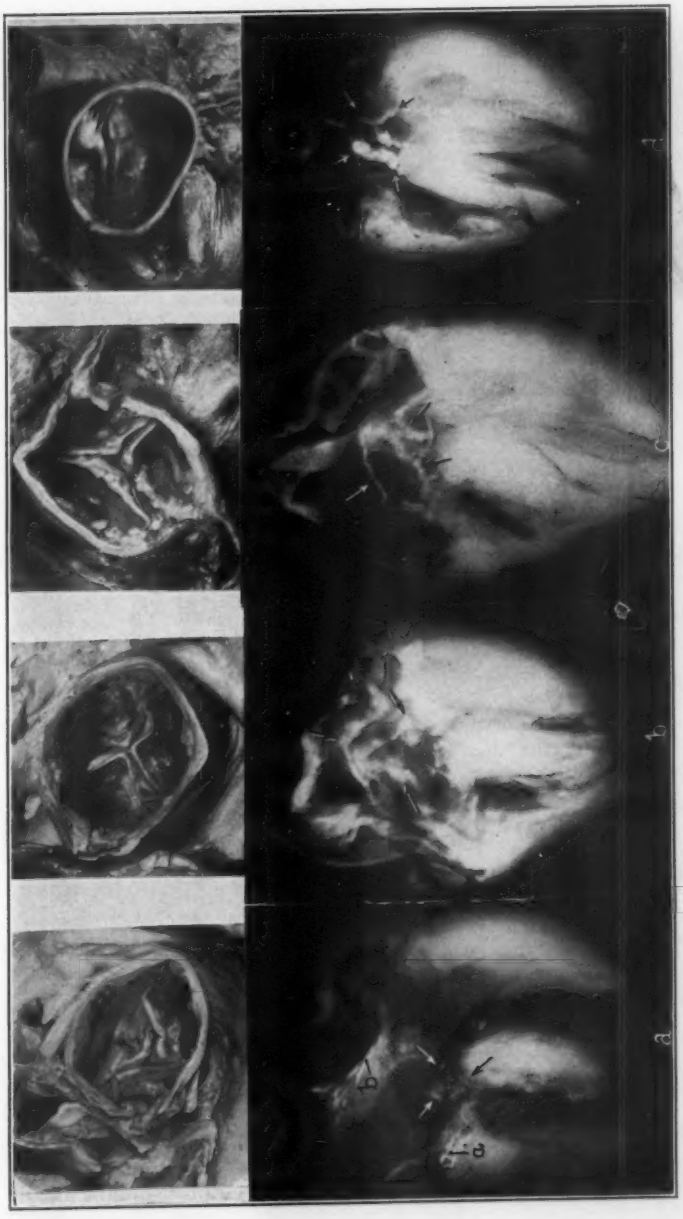

Fig. 2.—Gross and roentgenographic appearance of varying degrees of stenosis and calcification of the aortic valve. *a*, Stenosis and calcification, grade 1 [note minimal calcification of the aortic ring and leaflets indicated by arrows, and marked calcification in the coronary vessels (a) and aortic arch (b)]; *b*, stenosis and calcification, grade 2; *c*, stenosis and calcification, grade 3; *d*, stenosis and calcification, grade 4.

Associated Valvular Disease.—In many instances there were varying degrees of sclerosis and thickening of the leaflets of the mitral valve, with or without atheromatous plaques. Less frequently these changes were present in the other valves as well. Because they occurred as frequently among other individuals of the same age, no particular significance was attached to these changes. However, when there was shortening or fusion of the chordae tendineae and narrowing of the mitral orifice, we felt that we were dealing with definite evidence of healed rheumatic endocarditis. The degree of mitral stenosis varied from mild degrees to the classical "fish-mouth" type. On this basis, we found mitral stenosis present in fifteen cases, in twelve of which there was a history of rheumatic fever; endocarditis of the mitral and tricuspid valves was found in five cases, in two of which there was a history of rheumatic fever; endocarditis of the mitral, tricuspid and pulmonic valves was found in one case, in which there was also a history of rheumatic fever; and endocarditis of the tricuspid valve was found in one case.

Pericarditis.—In four cases there was an extensive obliterative type of adhesive pericarditis, in two of which there was a history of previous rheumatic fever. There was nothing to indicate that these cases of pericarditis were the result of secondary extension from suppurative disease of the lungs.

In all there were twenty-five cases (23.5 per cent) in which there was definite evidence of associated lesions representing the healed stage of rheumatic infection, a lower incidence than that associated with mitral stenosis (37 per cent).

Weight of Heart.—The weight of the heart in ninety-six of the 105 cases was recorded at necropsy. These weights are presented in Table I. Although no corrections were made for such factors as obesity and associated hypertension, it will be noted that in eighty-two cases (85.5 per cent) the heart weighed more than 400 gm.

TABLE I

WEIGHT OF HEART: NINETY-SIX CASES

HEART WEIGHT, GM.	200-299	300-399	400-499	500-599	600-699	700-799	800-899	900-999	1000+
Cases	1	13	24	25	11	11	7	2	2

Sclerosis of Coronary Vessels and Aorta.—Correlation of the degrees of stenosis and calcification of the aortic valve with the weight of the heart and with the degree of atherosclerosis of the coronary vessels and aorta is presented in Table II. The table is self-explanatory and substantiates again the observation previously made that sclerosis of the aorta and coronary vessels is likely to occur in inverse proportion to the degree of stenosis of the aortic valve. We wish to draw attention, also,

to the relatively short period between the onset of symptoms and final failure, particularly among the cases in which there was an associated mitral endocarditis.

TABLE II

CORRELATION OF DEGREES OF STENOSIS AND CALCIFICATION OF THE AORTIC VALVE WITH WEIGHT OF THE HEART AND WITH DEGREE OF ATHEROSCLEROSIS OF CORONARY VESSELS AND AORTA

CASES	AVERAGE AGE (YR.)	STENOSIS, AORTIC VALVE (GRADE)	CALCIFICATION, AORTIC VALVE (AVERAGE GRADE)	CORONARY SCLEROSIS (AVERAGE GRADE)	SCLEROSIS OF AORTA (AVERAGE GRADE)	WEIGHT HEART, AVERAGE (GM.)	DURATION SYMPTOMS, AVERAGE (YR.)	ASSOCIATED MITRAL ENDOCARDITIS, CASES
18	54.5	4	3+	1+	2	603	3.7	3
40	58.1	3	3+	2	2	526	2.0	14
45	62.6	2	2+	2	2+	477	2.9	9
3	66.0	1	1+	2	2+	428	0	0

Coronary Occlusion.—Acute coronary occlusion was encountered in but one case, and was the cause of death. In another case, there was a healed myocardial infarct. One additional case, that of a woman aged 66 years who had diabetes, requires special comment, in that she had experienced an attack which had all the characteristics of an acute coronary accident, including the classical electrocardiographic pattern and increased sedimentation rate; yet, when necropsy was performed there was no indication that such an event had occurred.

Causes of Death.—The causes of death may be summarized as follows: Thirty-two patients died of congestive heart failure (30.5 per cent). Eighteen patients died suddenly (17.0 per cent). Four of these patients had congestive failure and death occurred while the patient was under treatment. The response of each patient to therapy had been satisfactory up to the time of death. Five patients died of subacute bacterial endocarditis (4.7 per cent), one of acute coronary occlusion (0.9 per cent), and fifty died owing to causes not cardiac in origin (47 per cent).

It is noteworthy that, of the twenty-six patients who had associated mitral disease, the death of twenty-one patients (81 per cent) could be attributed directly or indirectly to the cardiac disease present. Thus, eleven patients died of congestive failure, five died suddenly, three died as a result of embolic phenomena, and two of superimposed subacute bacterial endocarditis.

It is also of interest to note that the majority of patients who died when the syndrome of congestive heart failure was present responded to therapy in a rather disappointing manner, compared with the response obtained from those who had congestive failure due to other causes. Symptoms are likely to remain in abeyance for many years, but with the

onset of myocardial failure the outlook becomes serious. One other aspect which influences prognosis considerably is the high incidence of sudden death of patients who frequently present little, if any, evidence of heart disease. In an attempt to gain further information with regard to the type of patient who is likely to die suddenly, we have analyzed critically the data relative to this group of cases, the details of which are presented in Table III.

TABLE III

PATIENTS WHO DIED SUDDENLY

NUMBER	AGE, YEARS AND SEX	POST-MORTEM FINDINGS				REMARKS
		STENOSIS, GRADE	CALCIFICATION, GRADE	WEIGHT OF HEART, GM.	CORONARY SCLEROSIS, GRADE	
1	63 M	3	3	586	3	Apparently good health
2	54 M	4	4	543	3	History of syncopal attacks
3	53 M	3+	3	520	3	Recent uneventful abdominal operation
4	62 M	4	4	646	–	History of angina pectoris
5	38 M	4	4	565	2	Apparently good health
6	79 M	3	4	740	4	Previous history not available
7	71 M	4	4	600	3	Healed infarcts; history of angina
8	57 F	3+	3+	x2	0	Dyspnea on exertion for one year
9	64 M	3+	3+	470	2	History of angina
10	64 M	3+	4	821	2	Calcification of aortic valve extended to coronary orifices. Number 10 gave a history of angina pectoris
11	29 F	4	4	573	0	
12	46 M	2+	4	970	0	
13*	45 F	2+	2+	360	2	Was being treated for congestive heart failure and was responding well to treatment before death
14	72 F	3+	3+	531	3+	
15†	46 M	3+	3+	892	1+	
16*	42 F	3+	3	655	0	
17	75 M	2	2+	550	3	Calculus of bladder removed six weeks before death
18*	56 F	3	3	434	1+	Thyroidectomy performed; doing well before death

*Associated mitral stenosis.

†Adhesive pericarditis obliterating two-thirds of pericardial cavity.

We wish to draw attention to the following facts arising from this analysis. 1. Fifteen of the eighteen patients who died suddenly had a marked degree of stenosis and calcification of the aortic valve. 2. In fourteen of the eighteen subjects, the heart weighed more than 500 gm., and in one other it was described as being twice the normal size. 3. Acute myocardial infarction was not responsible for the death of any of these patients. 4. Seven patients had severe coronary sclerosis. 5. Four patients gave a history of angina pectoris. 6. Three patients are of unusual interest in that, although coronary sclerosis was minimal or entirely absent, calcification of the aortic valve had extended to the region of the coronary ostia and was causing partial obstruction to flow of blood in the coronary vessels. Up to the time of their unexpected and sudden death, these patients had pursued their respective occupations. One of them gave a history of angina pectoris but others gave little, if any, history suggestive of much limitation of cardiac reserve.

CLINICAL DATA

Distribution According to Sex.—Group 1 was composed of eighty-eight men and eighteen women; group 2 was composed of sixty-eight men and twenty-two women; group 3 was composed of twenty-seven men and five women. In all, there were 183 men and forty-five women, a ratio of 4:1.

Distribution According to Age.—In group 1 (106 subjects on whom necropsy was performed), ages ranged from 22 to 87 years; the average was 58.8 years. The average age of the men was 63.4 years, ranging from 22 to 87 years. The average age of the women was 43.2 years, ranging from 29 to 72 years. The distribution by decades is illustrated in Table IV.

TABLE IV

DISTRIBUTION ACCORDING TO AGE

AGE	GROUP 1			GROUP 2			GROUP 3		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
20-29	3	2	1	4	2	2	0	0	0
30-39	5	4	1	12	8	4	2	1	1
40-49	20	16	4	15	12	3	3	2	1
50-59	24	19	5	24	18	6	11	10	1
60-69	30	24	6	20	17	3	12	11	1
70-79	20	19	1	14	10	4	4	3	1
80-89	5	5	0	1	1	0	0	0	0
Totals	106	88	18	90	68	22	32	27	5
Average total		58.8			53.6			59.4	
Average males		63.4			54.0			60.0	
Average females		43.2			51.4			56.4	

In group 2 (ninety patients studied clinically with confirmation of the diagnosis by fluoroscopic examination), the ages ranged from 23 to 86 years; the average was 53.6 years. The average age of the men was 54

years, ranging from 25 to 86 years. The average age of the women was 51.4 years, ranging from 23 to 78 years. The distribution by decades is illustrated in Table IV.

In group 3 (thirty patients studied clinically with confirmation of the diagnosis by fluoroscopic examination, but with findings on physical examination which were atypical), ages ranged from 38 to 78 years; the average was 59.4 years. The average age of the men was 60 years, ranging from 38 years to 72 years. The average age of the women, as in the other groups, was lower than that of the men, 56.4 years, ranging from 38 to 78 years. The distribution by decades is illustrated in Table IV.

STIGMAS OF PREVIOUS RHEUMATIC INFECTION (CLINICAL CASES)

Previous Rheumatic Infection.—Thirty patients belonging to group 2 and four patients belonging to group 3 gave a history of rheumatic fever. Together with the sixteen subjects belonging to the group on whom necropsy was performed, there were fifty patients in all (22 per cent) who had given a history of rheumatic fever.

Associated Valvular Disease.—Already we have mentioned that evidence of healed rheumatic lesions of one kind or another was found at necropsy in 23.5 per cent of cases of calcareous disease of the aortic valve. In group 2, a clinical diagnosis of associated mitral stenosis was made in six instances. Examination of three of these fluoroscopically gave evidence of calcification of mitral leaflets, although in three additional cases there was also fluoroscopic evidence of mitral calcification. Calcification of the mitral valve also was demonstrated fluoroscopically in two cases belonging to group 3.

Symptoms and Signs.—One of the striking features of the group as a whole is the insidiousness with which cardiac hypertrophy can reach gross proportions with little or no evidence clinically of interference with myocardial efficiency. This can only mean that the process of stenosis develops very gradually and that myocardial nutrition is maintained by an adequate coronary circulation. Our findings substantiate such a premise very strongly, and the clinical records reveal numerous instances of long-standing valvular disease in which the bruits discovered in earlier and repeated examinations corresponded with those which, years later, proved to be the result of calcareous disease of the aortic valve. Furthermore, there are instances in which the information was less accurate but in which the known presence of murmurs had covered a period of many years, in some cases, forty years or more.

When symptoms do arise, they are essentially those of myocardial insufficiency or of coronary insufficiency, a circumstance determined more by the process of stenosis than by associated disease of the coronary vessels and, as has been pointed out previously, the onset of symptoms in the majority of instances ushered in the final stages of the disease.

In Table V, the incidence of the individual symptoms is presented. It is to be recalled that group 1 is comprised of cases of all degrees of stenosis, that group 2 consists of cases in which there was clinical evidence of the more marked degrees of stenosis, whereas in group 3 there is reason to believe that we were dealing with less marked degrees of stenosis and, hence, we observed milder symptomatology and less typical physical findings. It will be noted that dyspnea was the most notable symptom indicative of a failing myocardium. Angina pectoris, when it occurred, was angina of effort, and in no instance did we encounter the prolonged type of anginal seizures which occur at rest among some individuals who are the victims of aortic insufficiency. The details regarding cases in which angina pectoris was a symptom are given in Table VI.

TABLE V

INCIDENCE OF SYMPTOMS

	GROUP 1, PERCENTAGE	GROUP 2, PERCENTAGE	GROUP 3, PERCENTAGE
No symptoms	29.1	21.4	50.0
Dyspnea	70.4	83.3	40.1
Angina pectoris	15.2	24.4	18.7
Syncope or vertigo	7.6	10.0	9.4
Congestive failure	32.4	31.1	12.5
Uncertain	6.6	2.2	9.4

Vertigo and syncope (at times epileptiform in character) were encountered infrequently and, in some, these manifestations were provoked by exercise, even in the absence of heart block.

The characteristic bruit and thrill associated with well developed calcareous stenosis of the aortic valve need no further description here; it is well known that, in addition, a regurgitant aortic murmur frequently is present. In our series an aortic diastolic murmur was recorded twenty-seven times in group 1, forty-eight times in group 2 and four times in group 3, that this, in 35 per cent of the entire series studied. This murmur is likely to be low-pitched, soft, and not easily audible. It is quite probable that in the earlier series comprising group 1 the diastolic murmur was present more frequently than the records indicate. It is not uncommon to find some variation in the intensity of the physical signs, particularly in the presence of a failing myocardium; among individuals who have emphysema the signs also may be obscured. Usually, both murmurs and thrills can be elicited more readily during full expiration with the patient leaning forward or after cardiac activity has been increased by gentle exercise.

Considerable attention rightly has been paid to the nature of the second aortic sound. From our clinicopathologic correlations, however, we feel certain that definite stenosis can be present when the second aortic sound is normal in character. When absent or considerably reduced, it can be concluded safely that the degree of stenosis is considerably advanced.

TABLE VI

CASES IN WHICH ANGINA PECTORIS WAS A SYMPTOM
DATA OBTAINED AT NECROPSY

NUMBER	AGE, YEARS AND SEX	CORONARY SCLEROSIS, GRADE	STENOSIS, GRADE	WEIGHT OF HEART, GM.	AORTIC REGURGITATION	CAUSE OR NATURE OF DEATH
1	64 M	2	2	470	0	Sudden
2	31 M	–	2+	700	+	Congestive failure
3	69 M	4	3	500	0	Congestive failure
4	58 M	3	2	1170	+	Congestive failure
5	64 M	2	3	821	0	Sudden
6	62 M	–	4	646	0	Sudden
7	74 M	2	2	428	0	Congestive failure
8	63 M	1+	3	611	+	Congestive failure
9	54 M	1	2	778	0	Uremia (hypertension)
10	79 M	3	4	480	0	Congestive failure
11	55 M	4	3	875	0	Congestive failure
12	76 M	1	3+	517	0	Postoperative prostatectomy
13*	65 F	3+	2	449	0	Diabetic gangrene
14	49 M	1	2	510	+	Congestive failure
15	56 M	3+	3	538	0	Coronary occlusion
16†	59 M	3	4	600	0	Sudden

*Symptoms and signs of acute coronary occlusion developed; not confirmed at necropsy.

†Healed infarct.

Size of the Heart.—The most eloquent expression of the almost constant presence of cardiac hypertrophy is afforded by 96 per cent of the subjects on whom necropsy was performed and the weight of the heart recorded. Remembering that stenosis varied from the mildest to the most extreme degree, it is of interest to note that in 85.5 per cent of the cases the heart weighed more than 400 gm. The term "heavy heart"[6] which has been applied in the description of these cases is very appropriate. There was definite clinical evidence of cardiac hypertrophy in sixty-eight of the ninety cases in group 2 and in seventeen of the thirty-two cases in group 3.

Electrocardiographic Findings.—In group 1, an electrocardiogram was recorded in sixty-three cases, in group 2 it was recorded in eighty-three cases, and in group 3 in twenty-eight cases. Thus, there was a total of 174 records for analysis. The details of this analysis are shown in Tables VII, VIII, IX, and X. The composite of Tables VII, VIII, IX, and X, and, thus, of the electrocardiographic findings as a whole, is shown in Table XI.

TABLE VII

ELECTROCARDIOGRAPHIC FINDINGS

NO SIGNIFICANT CHANGES IN T-WAVE

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	23	29	18	70
Regular rhythm	17	26	17	60
Auricular fibrillation	6	3	1	10
Left axis deviation	15	16	11	42
Right axis deviation	3	0	1 (sl.)	4
No preponderance	5	13	6	24
Delayed A-V conduction	2	1	0	3
Complete heart block	1	1	0	2
Bundle branch block	0	1	0	1

TABLE VIII

ELECTROCARDIOGRAPHIC FINDINGS

T-WAVE NEGATIVITY IN LEAD I OR IN LEADS I AND II (INCLUDING DIPHASIC T-WAVES)

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	23	29	7	59
Regular rhythm	19	23	7	49
Auricular fibrillation	4	6	0	10
Left axis deviation	20	24	4	48
Right axis deviation	0	0	1 (sl.)	1
No preponderance	3	5	2	10
Delayed A-V conduction	2	1	2	5
Complete heart block	0	2	0	2
Bundle branch block	2	5	1	8

TABLE IX

ELECTROCARDIOGRAPHIC FINDINGS

T-WAVE NEGATIVITY IN LEADS I, II, AND III (INCLUDING DIPHASIC T-WAVES)

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	10	16	1	27
Regular rhythm	9	15	1	25
Auricular fibrillation	1	1	0	2
Left axis deviation	4	4	0	8
Right axis deviation	0	2 (sl.)	0	2
No preponderance	6	10	1	17
Delayed A-V conduction	0	3	0	3
Complete heart block	0	0	0	0
Bundle branch block	1	0	0	1

TABLE X

ELECTROCARDIOGRAPHIC FINDINGS

T-WAVE NEGATIVITY IN LEADS II AND III (INCLUDING DIPHASIC T-WAVES)

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	7	9	2	18
Regular rhythm	6	7	2	15
Auricular fibrillation	1	2	0	3
Left axis deviation	2	1	1	4
Right axis deviation	4	2	0	6
No preponderance	1	6	1	8
Delayed A-V conduction	1	1	0	2
Complete heart block	0	0	0	0
Bundle branch block	0	0	0	0

TABLE XI

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS, 174 CASES*

	CASES	PER CENT	REMARKS
Regular rhythm	149	85	
Auricular fibrillation	25	15	In one case, auricular flutter alternated with auricular fibrillation
Left axis deviation	102	58.6	
Right axis deviation	27	15.5	
No preponderance	59	34	
No significant changes in T-wave	70	40.2	
Inversion of T-wave in Lead I or in Leads I and II	59	34	Including diphasic T-waves
Inversion of T-wave in Leads I, II, and III	27	15.5	Including diphasic T-waves
Inversion of T-wave in Leads II and III	18	10.3	Including diphasic T-waves
Disturbance of conduction	27	15.5	

*Composite of Tables VII, VIII, IX, and X.

Critical analysis of these electrocardiographic findings shows that they conform essentially to patterns consistent with established physical laws of electrocardiography. In short, an aortic lesion throws added strain on the left ventricle and, in most cases, this is indicated in the electrocardiogram by left axis deviation, and, should changes in the T-wave occur, Lead I or Leads I and II will be affected.[16]

Of special interest are the other cases in which, despite the presence of a mechanism capable of producing left ventricular strain and the conventional changes in the T-waves mentioned, there were changes either in all three leads or in Leads II and III. The latter group is dismissed easily, for we find that in the seven cases in which necropsy was performed and in which changes in the T-wave had occurred in Leads II and III, a complicating factor consistent with such a pattern was present in six. Thus, in four cases there was an associated mitral stenosis, and in one there was an advanced degree of pulmonary arteriolar sclerosis. The fact that the electrocardiograms of four of the five patients mentioned gave evidence also of right axis deviation confirms the contention that, in the differential effect on the two ventricles, right ventricular strain predominated. The electrocardiogram of the fifth patient gave evidence of left axis deviation, but he had taken digitalis to the point of vomiting and the changes in the T-wave in the second and third leads were undoubtedly the result of intoxication by digitalis. The sixth patient died as a result of extensive infarction involving the lateral wall of the left ventricle. There was also a healed infarct in the posterior basal portion of the left ventricle, providing again adequate explanation of the resulting electrocardiographic pattern. There are two records available in the seventh case. The first showed inversion of the T-wave in Lead III only, whereas in a second electrocardiogram, taken a few weeks later, the T-waves in both the second and third leads were inverted. This patient died as a result of widespread metastasis from carcinoma of the thyroid gland, but there was no evidence of metastatic involvement of the heart.

We were interested in studying the differential effect on the two ventricles caused by lesions involving both the aortic and mitral valves, including the cases of mitral stenosis associated with tricuspid endocarditis. There were twenty-two such records among the group of cases in which necropsy was performed. On electrocardiographic examination, left axis deviation had been noted in thirteen of these, of which seven showed changes in the T-wave in Lead I or in Leads I and II and only two showed changes in the T-wave in Leads II and III, one of which was the case already mentioned in which overdigitalization had occurred. In none of these thirteen cases was auricular fibrillation present. Right axis deviation had been noted in two cases, in both of which there was inversion of the T-wave in Leads II and III, conforming again to recognized laws of electrocardiographic behavior. In the remaining seven cases neither ventricle showed preponderance, and changes in the T-wave followed no special pattern. It is noteworthy that auricular fibrillation, which had occurred in five cases, was associated with either right axis deviation or with no preponderance of either ventricle, except in one case; this suggests that, as long as the left ventricle carries the major load, the auricles are far less likely to fibrillate than when the reverse is true.

In considering the ten cases in which necropsy was performed and in which changes in the T-wave had affected all three leads, mitral stenosis was present in four cases, and in one of these there was extensive adhesive pericarditis. In the remaining six cases there were no additional factors found which might have influenced the pattern of the T-wave. In this group of ten cases left axis deviation had been noted in only two; the remaining ones gave no evidence of preponderance of either ventricle.

Blood Pressure.—It has been commented on previously that the blood pressure seldom is elevated in this disease and that the pulse pressure is low, reflecting the effect of stenosis of the aortic orifice. Although this is essentially true in many instances, a survey of a large group of cases shows much variation in the height of both systolic blood pressure and pulse pressure; hypertension and aortic regurgitation constitute the main reasons for this variability. Differential analysis of blood pressure readings in the various groups which constitute our series is of interest. Thus, in group 1, which is composed of cases of all grades of aortic stenosis, the blood pressure of 38 per cent of the subjects had been more than 150 mm. Hg systolic or more than 90 mm. diastolic, and the readings of 62 per cent had been lower than these figures. In only three instances was the systolic blood pressure more than 200 mm. Hg. In correlating the blood pressure with the degree of stenosis, it is of interest to note that the average degree of stenosis in those cases in which high readings had been obtained was graded 2 (on the basis of 1 to 4) and, in 50 per cent of cases, the stenosis was graded 3 and 4 (but actually only three cases were graded 4), as compared with the average stenosis, graded 3,

in those cases in which low readings were obtained; in 66.6 per cent of these cases the stenosis was graded 3 and 4 (thirteen of which were graded 4).

In group 2, presenting clinical evidence of the more marked degrees of stenosis of the aortic valve, only 23 per cent had blood pressure readings higher than 150 mm. Hg systolic or 90 mm. diastolic, whereas 77 per cent had readings lower than these. In only two instances (2.2 per cent) was the systolic blood pressure found to be higher than 200 mm. Hg.

Finally, of the patients of group 3 (presenting clinical evidence of a lesser degree of stenosis of the aortic valve than that of group 2), fully 50 per cent had blood pressure readings higher than 150 mm. Hg systolic or 90 mm. diastolic, and three patients (10 per cent) had a systolic pressure higher than 200 mm. Hg.

It seems, therefore, that blood pressure is influenced, in a measure, by the degree of stenosis of the aortic valve, and that the height of the blood pressure bears an indirect relationship to the degree of stenosis of the aortic valve present, although it must be pointed out that, even if an extreme degree of stenosis of the aortic valve exists (confirmed at autopsy), it is possible to have severe forms of hypertension and all the associated changes in the peripheral vascular system that occur in cases of hypertension unassociated with disease of the aortic valve.

DISCUSSION

The evidence derived from the study of this material has led us to accept, unequivocally, rheumatic infection as the etiologic factor in calcareous stenosis of the aortic valve. During recent years, considerable confusion has resulted from the belief that stenosis of the aortic valve represented two types of lesions: the one identified as the rheumatic type, the other as the calcareous type. It is not without significance that, in the review of our complete material obtained at necropsy, no instance of stenosis of the aortic valve without some degree of calcification was encountered. The lesion does occur in young individuals who give a history of rheumatic fever and it occurs in association with mitral stenosis, a pathologic entity universally accepted as an unquestionable stigma of previous rheumatic infection, and indeed the incidence of single or repeated episodes of rheumatic fever, as revealed in the history of those who have a solitary lesion of the aortic valve, occurs far too frequently to represent merely a coincidence.

We must draw attention to the fact that both in Christian's group of twenty-one cases and in the group of forty-two cases reported by Margolis and others,[17] only hearts which on examination did not show evidence of associated valvular disease were accepted for study, and it is obvious that, in this discriminate selection, the very cases which bear the appropriate etiologic label (in the form of healed mitral endocarditis) were excluded from their respective series. Both of these

studies were made in 1931, before the knowledge on which much of this paper is based was available. Christian's contention, nevertheless, was that the disease was of rheumatic origin.

That deposition of calcium should occur in a region of low vascularity, from which inflammatory products cannot be absorbed adequately, is an expression of the phenomenon of calcification in general. The leaflets of the heart valves satisfy this set of circumstances perfectly.

There are several apparent objections to such an explanation. Firstly, it may be argued, why does not calcification occur universally in all healed rheumatic lesions? And secondly, why does the striking discrepancy as regards sex occur if rheumatic fever attacks both sexes without any appreciable discrimination? Or again, why should the clinical manifestations and the life history of calcareous disease of the aortic valve diverge so widely from those of the conventional forms of rheumatic carditis? The fact that it differs in its clinical behavior, in many respects, from the more classical varieties of rheumatic heart disease is not an argument against its rheumatic origin. Every other smouldering form of chronic inflammatory disease, such as tuberculosis and syphilis, is associated with the same variability in its clinical course as well as in its predilection for certain tissue, which varies from case to case. We wish to present an hypothesis which answers these questions. It is based on the belief that rheumatic infection which culminates in calcareous disease of the aortic valve differs only in a quantitative manner, and not in any qualitative manner, from other types of rheumatic carditis.

Rheumatic infection which eventually culminates in calcareous stenosis of the aortic valve was originally a mild form of rheumatic carditis which had allowed both the mitral valve and the myocardium to escape with minimal or no damage. By the same token, we must assume that although the incidence of rheumatic fever is more or less equal in the two sexes women do not share the same relative immunity to more serious and widespread involvement as often as men. The gradual sclerosing process characteristic of rheumatic valvulitis which follows, and fusion of the cusps, which is part and parcel of the inflammatory reaction, have now set the stage for a very gradually developing stenotic process, a condition which satisfies the pathologic requisites for a similar, gradually progressing deposition of calcium. In the study carried out by Clawson and his co-workers, 84 per cent of all nonsyphilitic deformities of the aortic valve were found to contain calcium on gross examination.

Thus time and a relatively efficient coronary circulation (in the early stages, at least) are the main factors which allow cardiac hypertrophy to proceed so surreptitiously that a heart of 800 gm. is found unexpectedly in a patient dying from an unrelated disease whose previous history revealed little, if any, evidence of limitation of cardiac reserve. It is

this factor of time which explains why calcification need not be a universal concomitant of healed rheumatic lesions, because those harboring the more serious forms of the disease, especially when accompanied by mitral stenosis, are weeded out by death before such an event as calcification can occur, thus leaving the solitary aortic lesion, one that the heart tolerates far better than mitral stenosis,[18] to continue for a long time without embarrassing the cardiac reserve.

Finally, the very fact that a history of rheumatic fever cannot be elicited more frequently than in 22 per cent of cases substantiates the hypothesis that the original acute inflammatory episode was mild and, perhaps, was so atypical that its significance could not have been realized at the time of its occurrence.

Our material was derived largely from the middle western states where conditions are relatively less favorable for the occurrence of rheumatic fever and where, on the whole, mild and atypical forms of the disease may be anticipated. It is possible that surveys in regions where the disease is more prevalent may show a relatively lower incidence of calcareous disease of the aortic valve.

SUMMARY

Calcareous disease of the aortic valve is not rare. We found that it constituted 18.1 per cent of all healed valvular defects. The criteria heretofore outlined for clinical recognition of calcareous stenosis of the aortic valve apply only to the advanced forms of the disease. However, the physical signs of even minimal and moderate degrees of calcareous stenosis and calcification of the aortic valve are sufficiently clearly defined to allow of clinical recognition, especially because it is possible to obtain confirmation by expert fluoroscopic means during the life of the patient. The frequency with which a history of rheumatic fever is obtained and stigmas of rheumatic infection are found is too great to be regarded merely as a casual and not a causative factor. There is convincing evidence that the lesion may be present in a clinically recognizable form for many years. Its very gradual progression, however, speaks for an initially mild valvulitis with even less involvement of the myocardium and of the other valves. Cardiac hypertrophy is present in a high percentage of cases and closely parallels the degree of aortic stenosis. Atherosclerosis of the coronary vessels and aorta occurs in inverse proportion to the degree of stenosis of the aortic valve, and coronary occlusion is extremely rare. Angina pectoris, however, is frequently a symptom and seems to depend more on the stenotic process than on coronary sclerosis.

Death is associated with congestive failure in about a third of the cases. Sudden death occurs in about a fifth of the cases and, in considering all grades of stenosis, death results from noncardiac causes in about half of the cases. The presence of mitral stenosis seriously mili-

tates against maintenance of cardiac function. The more mitral stenosis plays a part, the closer will the case conform to the more conventional forms of rheumatic heart disease. Blood pressure and pulse pressure readings need not be low. Well-recognized laws of electrocardiographic behavior determine the electrocardiographic pattern in calcareous disease of the aortic valve. Auricular fibrillation is relatively rare when the electrocardiogram gives evidence of predominance of the left ventricle.

The prognosis varies considerably, depending largely on the degree of stenosis and on the presence of complicating factors, especially mitral stenosis. Absence of the second aortic sound usually means that marked stenosis exists.

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AN EVALUATION OF HEART VOLUME DETERMINATIONS BY THE ROHRER-KAHLSTORF FORMULA AS A CLINICAL METHOD OF MEASURING HEART SIZE

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FOR some years roentgenologists, particularly in Italy and Germany, have been interested in clinical methods of cardiac measurement by which heart size might be determined more accurately than by the standard methods of the cardiothoracic ratio or the area of the frontal silhouette. It is agreed that the theoretical ideal for estimating the size of the heart is by determining its volume. Both the cardiothoracic ratio and the frontal cardiac area are measurements limited to one plane, while reliable volumetric determinations require measurements in at least two planes and theoretically should give a better concept of heart size. The clinical possibilities of such a method have received little attention either in this country or abroad and, consequently, it seemed desirable to evaluate the practical application of volumetric estimations of heart size in order to determine whether such a method would offer any advantage to the clinician over the present routine roentgenographic measurements of the heart.

MATERIAL

The material upon which this study is based consists of 100 adult males and seventy adult females with clinically normal hearts and forty individuals with heart disease. The normal material was gathered from ambulatory patients in either the medical or surgical wards or the outpatient department of the Massachusetts General Hospital and from a group of healthy subjects. The majority of the hospital patients were in a good state of general health. Since the age in the normal group ranged from the second through the sixth decades of life, and since electrocardiograms were not taken routinely, it is possible that some of the older individuals may have had slight, unrecognized coronary disease, but none had any symptomatic or physical evidence of heart disease. The group with abnormal hearts consisted mainly of individuals with the more common cardiac lesions.

METHOD

Reconstruction of the heart in plastic material from orthodiagraphic tracings taken in different planes is unquestionably the most accurate method of determining heart size, the volume of the heart being measured by water displacement of the model. The technique for this procedure has been described by Palmieri.[1] Accurate as this method may be, it is obviously impractical for clinical use.

The alternative is a mathematical formula, of which several have been devised.[2-6] In this study we have employed a formula first described by Rohrer,[5] in 1916, and, interestingly enough, again independently by Kahlstorf,[4] in 1932.

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The theoretical basis for the formula rests in the fact that the shape of the heart in general can be considered to be halfway between that of a paraboloid and an ellipsoid. The volume of these bodies can be determined mathematically with an error of ± 4 per cent by the following formulas: ellipsoid, $V = A \times D \times c$ (0.667); paraboloid, $V = A \times D \times c$ (0.59). A is the surface area of a parallel projection of the body being studied; D, greatest depth diameter in the direction of projection; c, constant.*

Transferring these formulas to the heart, the heart volume can then be approximated by the product of the area of the frontal cardiac silhouette and the greatest horizontal depth of the heart in the lateral position, multiplied by a constant. For the heart this constant would be theoretically halfway between those for the paraboloid and the ellipsoid, i.e., 0.63. In practice this constant may be varied in either direction, as the shape of the individual heart resembles more closely either the ellipsoid or the paraboloid. In this study, however, we have not complicated matters by introducing such an individual variable and have employed only the constant 0.63.

The teleoroentgenographic apparatus to be described in the AMERICAN HEART JOURNAL, by Liljestrand, Lysholm, Nylin, and Zachrisson for obtaining the measurements necessary to calculate the heart volume should give slightly more constant results than fluoroscopic measurements. The construction of such an apparatus, however, is hardly practical except for purely experimental purposes. Since we were interested in the practical application of the heart volume formula, we have employed orthodiagraphic measurements. The technical procedure for obtaining these measurements follows.

The individual was seated and the frontal orthodiagram was made in the usual manner. The subject was then rotated 90° to the left and both hands placed on the head. The lateral silhouette of the heart, in so far as it was possible with any degree of accuracy, and the ventral aspect of the sternum were then traced. The esophagus was filled with barium in some cases to help locate the posterior border of the heart. Three separate tracings were made in this position for reasons to be discussed later. The cardiac silhouette of the frontal orthodiagraphic tracing was then completed and the area computed in square centimeters with a planimeter until two determinations checked closely. The greatest horizontal depth diameter was measured in centimeters and the average of the three separate determinations was taken as the depth measurement. The heart volume was not estimated in instances where great discrepancies (over 6 mm.) existed between individual depth measurements. Orthodiascopy was employed exclusively, and the entire procedure from the beginning of fluoroscopy to the computation of the heart volume consumed approximately 15 minutes. The heights of the subjects, without shoes, were determined in centimeters and their weights, with the heavier articles of clothing removed, in kilograms. All percentages in the tables were computed to the nearest significant number and in such a way that the maximum percentage variation would be obtained.

SOURCES OF ERROR IN THE METHOD

Benedetti and Bollini[7, 8] have discussed volumetric formulas other than their own from the anthropometric standpoint; the main objection to formulas other than that of Bollini is that they do not take into consideration the position of the heart in the thoracic cage as a factor influencing the shape of the heart shadow. There is no doubt that the formula of

*The following abbreviations are used in the tables. *A*, frontal cardiac area. *D*, greatest horizontal depth diameter of the heart in the lateral position. *V*, cardiac volume. *T*, transverse diameter of the heart. *Th*, transverse diameter of the thorax. *CTR*, cardiothoracic ratio.

Bollini[3] has been more carefully controlled by comparisons with the actual volume of models and gives theoretically a more accurate estimation of the actual heart volume. We considered, however, that the technical difficulties and errors entailed in tracing accurately the complete lateral silhouette of the heart and in determining the point of bifurcation of the trachea necessary for this formula made this method less suitable and not significantly more accurate in practical application than the simpler Rohrer-Kahlstorf formula. Before discussing the technical errors of the Rohrer-Kahlstorf method, which has been our principal interest, we wish to bring out two objections which apply more or less generally to all mathematical formulas for estimating heart volume.

Firstly, the heart varies so in shape normally that no one mathematical formula can be expected to be generally applicable and to allow an accurate determination of the volume of the heart actually to be measured. While Bollini has in part compensated for this variable by considering the position of the heart in the thorax, there still exist exceptions wherein his formula would be in considerable error. Secondly, it is well known that in heart disease there is very often a predominant enlargement of one chamber of the heart, most commonly the left ventricle or the left auricle. Mathematical formulas in general must consider the heart as a whole, and do not allow for the disproportionate enlargement which takes place in heart disease. It is obvious that such disproportionate enlargement may so affect the necessary orthodiagraphic measurements that they are not justifiably applicable in a method which is theoretically based on a concept of the heart as a more or less uniform geometrical body. For example, in mitral stenosis the enlargement of one chamber, the left auricle, can markedly increase the depth diameter so that a significant error may easily result in the application of such a formula.

Both Rohrer and Kahlstorf placed the maximum error in the formula at ± 15 per cent. Kahlstorf orthodiagraphed formalin-fixed anatomic specimens and compared the volumetric estimation by formula to the volume by water displacement of the specimen. On the results from nine normal and three pathologic hearts he concluded that the maximum error inherent in the formula was ± 5 per cent. Bollini, using heart models made by Palmieri's method and comparing the calculated results by the Rohrer-Kahlstorf method to that by water displacement of the model, found the error to vary from –1 per cent to +16 per cent in twenty normals and from +4 per cent to +42 per cent in ten pathologic hearts. From these figures it is obvious that the error may be negligible or, on the other hand, so great, particularly in diseased hearts, as to invalidate the determination.

Kahlstorf further concluded that maximum additional technical errors of ± 5 per cent each resulted from the determination of the frontal area of the heart and from the measurement of the depth diameter. In estimating the cardiac area of the frontal orthodiagram the source of error

lies almost entirely in completing the cardiac contour of that part of the heart shadow which merges with the aorta above and the portion of the heart which is hidden by the diaphragm below. Roesler[9] states that the variations in completing the frontal orthodiagraphic tracing for the estimation of the cardiac area on different days by the same individual range from 2 per cent to 5 per cent, and when different individuals complete the same tracing the variations may reach 20 per cent. Table I shows cardiac area determinations on seven different frontal orthodiagrams computed on three different days by each of three individuals of varying experience. It can be seen that both experience and heart size make a slight difference. It is true that the tendency to error is less in small and vertical hearts than in hearts which are transverse in position. The reason for this is illustrated in Figs. 1 and 2, which show that the amount of the cardiac silhouette to be completed arbitrarily is considerably less in the vertical type of heart. It is safe to say from our results that with experience, no matter what the heart size may be, the individual error in completing the cardiac silhouette will be less than 5 per cent. Further, it would seem that even between different individuals the percentage variation will be, as a rule, less than 10 per cent, although on occasions it may rise as high as 12 to 15 per cent.

TABLE I

FRONTAL CARDIAC AREAS ESTIMATED FROM TRACINGS OF SEVEN DIFFERENT ORTHODIAGRAMS BY THREE INDIVIDUALS OF VARYING EXPERIENCE ON THREE DIFFERENT OCCASIONS

	FRONTAL CARDIAC AREAS							
	1	2	3	4	5	6	7	AVERAGE
A. (Experienced)	67.3	83.8	94.3	112.0	116.5	130.0	174.6	
	68.6	84.4	92.2	114.8	115.0	123.6	182.3	
	67.2	84.3	91.2	110.4	111.0	124.3	178.0	
Percentage of difference	2	1	3	4	5	5	4	3
B. (With slight experience)	70.4	85.2	97.6	115.4	117.0	123.1	184.8	
	69.1	85.2	97.7	110.1	115.6	137.4	173.6	
	70.1	87.8	97.0	110.1	117.5	130.2	180.8	
Percentage of difference	2	3	1	5	2	12	6	4
C. (With no experience)	68.0	85.0	92.3	111.2	114.3	129.9	176.1	
	65.4	82.5	90.8	109.8	105.2	123.0	170.6	
	66.7	84.4	91.3	110.8	108.3	124.3	169.6	
Percentage of difference	4	3	2	1	9	6	4	4
Percentage difference A-B	5	5	7	5	6	11	6	6
Percentage difference A-C	5	2	4	5	11	6	7	6
Percentage difference B-C	8	6	7	5	12	12	9	8

By far the most unsatisfactory measurement is that of the depth diameter, and consequently we found that the average of three separate determinations was more accurate than a single measurement. By discarding those determinations in which this measurement varied by more than 6 mm., the error was automatically limited to approximately 6 per cent for an individual volumetric determination. The ventral point for this

measurement is usually the manubrium just below its contact with the right ventricle. As a rule there is little difficulty in establishing the position of this point by fluoroscopy, although at times even the manubrium is not so clearly seen as might be expected. To locate fluoroscopically the posterior border in the lateral position, however, is frequently extremely difficult. This is particularly the case with large or transverse hearts when the retrocardiac space is obliterated, with a consequent loss of contrast. Not infrequently hilar vessel shadows, a thick chest, or obesity diminish the radiolucency of the retrocardiac space and add to the difficulties in locating the posterior cardiac border even when the heart is relatively small.

Fig. 1.

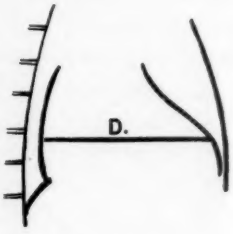

Fig. 2.

The most interesting and significant of our results are to be found in Table II. The heart volume in the same individual was determined on three successive days at approximately the same time of day (controlling the conditions by fluoroscoping the subject before breakfast made no significant difference). The percentage variations between the minimum and maximum figures for the horizontal depth diameter, the frontal cardiac area, and the heart volume can be readily seen. From the technical point of view it seems safe to say that the percentage error will be usually less than ±10 per cent in those hearts whose volumes are 700 c.c. or less, while a percentage error of ±10 per cent to ±20 per cent may result in those hearts whose volume is greater than 700 c.c. In other words, the maximum technical error for normal hearts will be, in general, ±10 per cent, while for diseased hearts with enlargement of any degree the percentage error varies considerably and may be as high as ±20 per cent.

TABLE II

CARDIAC VOLUMETRIC DETERMINATIONS MADE BY ONE OBSERVER ON THREE SUCCESSIVE DAYS IN SEVENTEEN INDIVIDUALS

CASE NO.	D_1	D_2	D_3	% DIFF.	A_1	A_2	A_3	% DIFF.	V_1	V_2	V_3	% DIFF.
51	7.5	7.1	7.4	6	64.5	66.8	67.3	4	305	299	314	5
216	7.8	7.5	7.0	11	79.0	79.4	78.2	2	388	375	345	12
54	8.5	8.3	8.5	2	86.4	84.5	80.6	7	463	442	432	7
127	8.4	8.2	8.3	2	92.9	97.8	98.2	6	491	505	513	4
184	7.9	8.2	8.1	4	89.1	95.1	91.1	7	443	491	465	11
154	8.3	8.6	8.4	4	108.6	107.2	112.5	5	568	581	595	5
152	8.7	9.4	8.7	8	106.8	105.5	108.3	3	585	625	594	7
153	8.2	8.4	8.0	5	115.7	112.9	114.5	2	598	597	577	4
132	10.5	9.6	9.6	9	98.0	97.4	93.5	5	648	589	565	15
*126	9.2	9.1	9.3	2	110.4	110.1	107.1	3	640	633	627	2
133	10.1	9.2	9.8	10	100.0	105.3	113.7	14	636	610	702	15
188	8.9	9.1	9.3	5	110.5	112.0	100.5	11	620	642	589	9
*193	9.3	10.6	9.7	14	129.5	122.3	114.3	13	759	817	698	17
196	10.5	9.7	9.5	11	122.0	120.2	120.0	2	807	742	749	9
198	11.0	11.1	11.4	4	119.7	126.3	123.1	6	829	883	884	7
*213	12.0	11.6	11.2	7	158.1	154.5	147.2	7	1195	1139	1039	15
*183	12.5	12.1	13.0	7	204.3	207.8	232.6	13	1609	1584	1905	20

*Heart disease.

In summary, then, it can be concluded on the basis of Bollini's[3b] figures from heart models that with the Rohrer-Kahlstorf formula the estimated volume may vary from the actual volume by extremes of –1 per cent and +16 per cent, to which may be added a maximum technical error of ±10 per cent in clinical application if the heart volume is less than 700 c.c. The total extremes, then, in normal hearts of less than 700 c.c. would be –11 per cent and +26 per cent. From the latter figures it would seem justifiable to conclude that except for occasional instances the volume of normal hearts can generally be estimated by the Rohrer-Kahlstorf formula with a maximum error of ±15 per cent, as originally stated by these authors. Since the variation from the actual volume in enlarged hearts, according to Bollini, varies from +4 per cent to +42 per cent, and the maximum technical error for hearts of all sizes is ±20 per cent, it follows that the extremes of error by the Rohrer-Kahlstorf method for enlarged hearts is theoretically –16 per cent and + 62 per cent. Obviously, such results make the method of questionable value when cardiac enlargement is present.

THE HEART VOLUME IN NORMAL SUBJECTS

The data concerning the normal hearts revealed several points of interest. The range of the heart volume in males was from 400 c.c. to 900 c.c. Only eleven subjects, however, had heart volumes of over 700 c.c. The latter were all heavy, stocky individuals, and the measurements on those with heart volumes over 800 c.c. might well be questioned because of the technical difficulties. In females the range of heart volume was from 300 c.c. to 550 c.c., except for five heavy individuals.

Fig. 3 shows the variations in normal heart volume and the existence of a very definite linear correlation between heart volume and body

weight and body surface area. This is in agreement with anatomical studies on heart weight and clinical studies with various cardiac measurements, in which it has been found that of the various body measurements the closest correlation exists between body weight and heart size. As Kahlstorf found, there was in our series no parallelism between body height and heart volume.

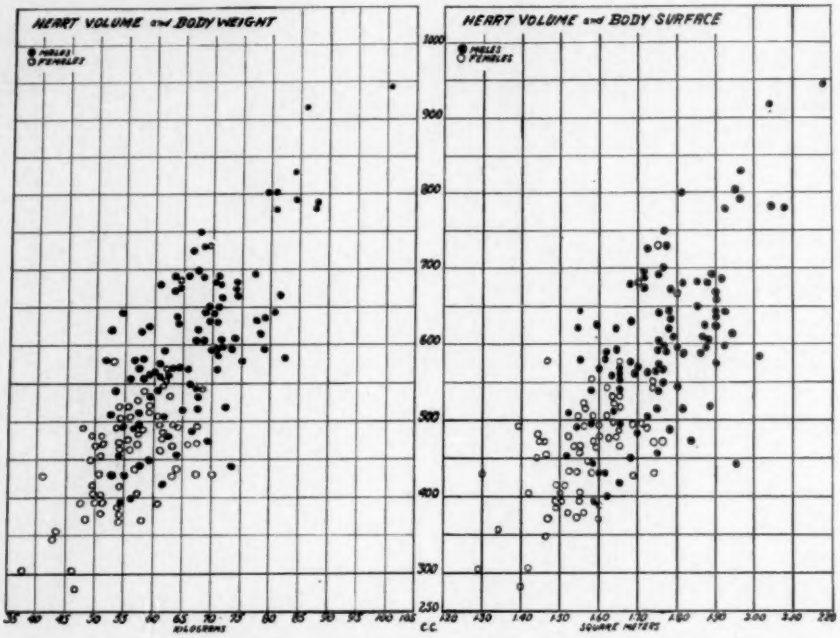

Fig. 3.—Graphs showing the correlation between heart volume and body weight and body surface area in 170 individuals with normal hearts.

Unfortunately, the body-weight, heart-volume correlation is not sufficiently close to warrant its use as a criterion for establishing normal values. From the graphs it can be seen that two individuals of the same weight may have heart volumes which vary by as much as 200 c.c. It is clear that the smaller heart could enlarge rather markedly before it would fall beyond the limits of normal as established by an index based on the body-weight, heart-volume correlation.

THE HEART VOLUME IN INDIVIDUALS WITH HEART DISEASE

It is not an uncommon experience to find individuals in whom the cardiothoracic ratio or the area of the frontal cardiac silhouette is abnormal, and in whom there are slight or equivocal findings which may or may not be indicative of heart disease. If the heart is transverse in position the situation is further confused and the abnormal measurements still more difficult to interpret. This was the group which we originally hoped to be able to clarify by the heart volume estimations. It soon became evident, however, that the boundary between normal and

abnormal heart size by this method was too wide and, further, that the position of the heart in the individuals of this group was usually transverse and, as a result, the volumetric determination more liable to technical error.

In view of the large potential theoretical error in diseased hearts we concluded that little was to be gained by an exhaustive study of subjects with heart disease. The examination of diseased hearts revealed some points of interest and one positive conclusion. The largest heart was found in a case of mitral and tricuspid stenosis, in which the volume was over 3,500 c.c. The smallest abnormal heart volume (350 c.c.) was found in a patient with long-standing chronic colitis with cachexia who had electrocardiographic changes indicating myocardial disease.

TABLE III

TYPE OF HEART DISEASE	NO. OF CASES	MINIMUM VOL.	MAXIMUM VOL.
Coronary	8	614	874
Hypertensive	6	623	1543
Valvular disease			
1. Aortic regurgitation	11	633	1417
2. Mitral stenosis	5	479	1009
3. Aortic regurgitation and mitral stenosis	3	673	1510
4. Aortic stenosis	2	825	933
5. Mitral and tricuspid stenosis	1		3503
Miscellaneous	4	896	1609

As might be expected, there was a considerable variation of the heart volume in heart disease (Table III), particularly in those individuals with valvular disease and hypertensive heart disease. This is to be expected, since the heart size in individuals with valvular disease will depend upon the type, severity, and duration of the valvular lesion, while in the hypertensive group the degree of hypertension and the duration will be the important factors in determining the extent of cardiac enlargement.

TABLE IV

CARDIAC MEASUREMENTS MADE ON AN INDIVIDUAL WITH HEART DISEASE AT DIFFERENT PERIODS DURING CLINICAL IMPROVEMENT

	T	TH	CTR	D	A	V
5/27/37	17.5	26.5	66%	12.6	164	1303
7/ 9/37	16.8	26.4	64%	10.8	188	1279
8/19/37	14.8	26.4	56%	10.6	147	983
10/13/37	14.4	26.2	55%	9.6	140	852

A significant point was brought out by the study of a patient with cardiac enlargement of undetermined etiology. This patient was followed, at intervals, from the time of admission with heart failure, through convalescence, and for a period during which he was carrying on a relatively normal life. Table IV shows the gradual diminution in

heart size, which is much more strikingly shown by the heart volume estimation than by any of the other cardiac measurements. It would have been interesting to follow a series of individuals with heart failure before and after treatment. However, the opportunity to make such comparisons without discomfort and possible harm to the patient does not present itself frequently. It is clear that both the theoretical and technical errors would be relatively constant when volumetric estimations are made on the same heart, so that the major objections to the use of the formula would be largely eliminated. By the use of the volume figure in such a manner we believe that a better concept is obtained of the actual increase or decrease in heart size either during a period of heart failure or in following a patient over a period of years.

SUMMARY AND CONCLUSIONS

1. The heart volume (in cubic centimeters) as estimated by the Rohrer-Kahlstorf formula (area in square centimeters of the heart shadow in the frontal silhouette times depth in centimeters in the lateral silhouette times 0.63, a constant) was determined in 100 adult males and seventy adult females with clinically normal hearts. The heart volume was also estimated in forty individuals with the more common cardiac abnormalities.

2. The theoretical basis for the formula is discussed and its clinical application is described.

3. The percentage of error in the practical application of the Rohrer-Kahlstorf formula is estimated by combining the inherent error in the formula as determined by Bollini (through comparison of the computed heart volume by formula, with the actual heart volume of heart models by water displacement) and the maximum technical error as determined by our results. In normal hearts the error varies from –11 per cent to +26 per cent, so that with only a few exceptions the maximum error will be within ±15 per cent, as originally stated by both Rohrer and Kahlstorf. In enlarged hearts the error varies widely from –16 per cent to +62 per cent, so that the method cannot be applied with any degree of accuracy in many instances of cardiac enlargement.

4. The volume of normal hearts ranged from 400 c.c. to 900 c.c. in males, and from 300 c.c. to 550 c.c. in females. Only eleven males, however, had heart volumes over 700 c.c., and those over 800 c.c. may well be questioned because of technical difficulties. A linear correlation was found to exist between heart volume and body weight and body surface. This correlation, however, was not sufficiently close to allow the derivation of a reliable index as a criterion for normal, inasmuch as the normal range was from 6 c.c. to 12 c.c. per kilogram of body weight and from 200 c.c. to 450 c.c. per square meter of body surface (males 6.7 to 11.8 c.c. per kilogram, and 250 to 450 c.c. per square meter; females 6.1 to 10.6 c.c. per kilogram and 200 to 435 c.c. per square meter). No parallelism was found between body height and heart volume.

5. The diseased hearts showed a wide range of heart volumes. The largest was 3,500 c.c. in a case of mitral and tricuspid stenosis, the smallest 350 c.c. in a case of cachexia due to chronic colitis in which the electrocardiogram showed evidence of coronary insufficiency or myocardial disease. The changes in heart volume were followed in one case through a period of heart failure and during convalescence. Since the percentage of error would be relatively constant when determinations are made on the same heart, and since the volumetric figure gives a better concept of actual heart size, it is believed that there is a definite advantage in using volumetric estimations to follow the changes in the size of the heart in individual patients through a period of heart failure or over a period of years.

6. In general we must conclude that the volumetric estimation of heart size is no more reliable by itself than are other heart measurements. It is true of volumetric determinations as of heart measurements of any kind that, due to their wide normal variation, they must be interpreted in relation to the impression arrived at during fluoroscopy and, particularly when measurements are questionable, in relation to the expected normal position (vertical or transverse) and shape of the heart in the thorax. It should be recognized that the position of the heart and its normal size and shape depend largely upon body build and occasionally upon an abnormality of the thoracic cage itself; it is always important to consider these factors in the interpretation of heart size and measurements. Further study of the correlation of heart size and shape with various anthropometric measurements other than weight, height, and body surface may yield formulas more reliable and useful than exist at present. We are contemplating the pursuit of such a study.

Addendum: The paper by Liljestrand, Lysholm, Nylin, and Zachrisson, to appear in the AMERICAN HEART JOURNAL, entitled "The Normal Heart Volume in Man," confirms the conclusions noted by us concerning the present unsatisfactory basis for the determination of normal heart volume. They found, as we did, a wide variation of the normal, 7.0 to 13.0 c.c. of heart volume per kilogram of body weight and between 250 and 490 c.c. per square meter of body surface, in 101 healthy men whose ages ranged from 21 to 47 years.

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THE EFFECTS OF ALKALOSIS AND OF ACIDOSIS UPON THE HUMAN ELECTROCARDIOGRAM*†

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MUCH attention has been given to electrocardiographic changes caused by heart disease or by drugs used in the treatment of heart disease. Little notice has been taken of transient changes not related to heart disease. It has long been known that such changes may be caused by exercise,[1] drinking iced water,[2] stimulation of the vagus or sympathetic nerves,[1, 3, 4] and by alterations in the position of the heart such as may be produced by respiration or changes in posture.[1, 5]

There have been a few observations upon the effects of alkalosis and of acidosis upon the electrocardiogram. In 1926, Schott[6] reported that in dogs the T-waves may be made taller by giving hydrochloric acid intravenously, and smaller by giving sodium carbonate intravenously. Transient reduction in the amplitude of T in man during the tetany of spontaneous overbreathing was reported in 1929 by Kronenberger and Ruffin,[7] and in 1932 by McCance.[8] Simpson[9] has observed reduction in the amplitude of T in patients undergoing artificial fever therapy, all of whom had alkalosis.

An increase in the duration of electrical systole (the Q-T interval) in man has been observed by Bazett[10] following exercise, and by Carter and Andrus[11] in alkalosis. Samojloff[3] and Bazett noted an increase in the duration of systole after giving atropine. In various conditions in which the blood serum calcium is reduced the duration of electrical systole is increased,[11-14] while an elevation of serum calcium may be accompanied by a reduction in the duration of electrical systole.[12, 13, 15]

The present study was prompted by the observation of T-wave changes occurring during an episode of hysterical overventilation with tetany.

CASE REPORT

The patient was a 23-year-old male medical student who was conscious of his heart beat, but who showed on physical and electrocardiographic examination on May 16, 1923, no evidence of cardiac abnormality (Fig. 1 *A*). On Dec. 20, 1923, he was admitted to the hospital complaining of difficult breathing and cramping pains in the abdomen and extremities. Examination showed deep and rapid breathing and the typical carpopedal spasm of tetany, but revealed no abnormality of the heart or lungs. An electrocardiogram, however, showed pronounced flattening of the

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T-waves (Fig. 1 *B*). When the patient was reassured and persuaded to breathe normally his symptoms rapidly disappeared, and on the following day his electrocardiogram was normal (Fig. 1 *C*), resembling that of May 16.

Although it was thought that the patient had hysterical overventilation, the question remained as to whether he might have had a transient cardiac condition which caused the dyspnea and the T-wave changes, or whether overventilation was responsible for the changes in the electrocardiogram.

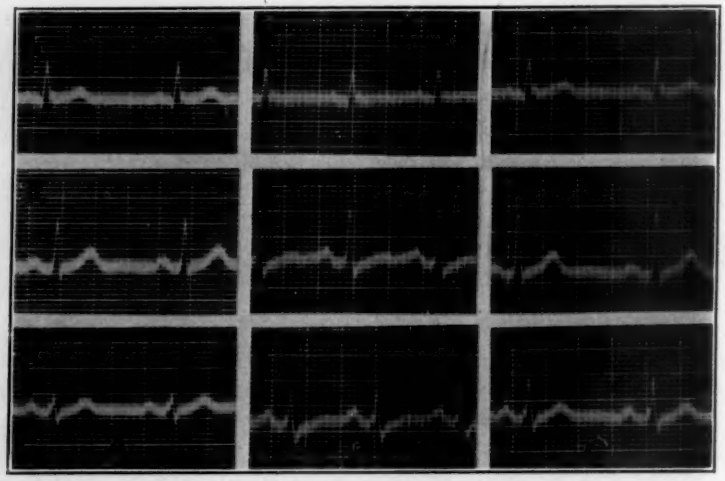

Fig. 1.—Electrocardiograms of patient. *A*, May 16, 1923. *B*, Dec. 20, 1923, during hysterical overventilation. *C*, Dec. 21, 1923.

EXPERIMENTAL OBSERVATIONS

In this study seven normal young adults served as subjects for forty experiments. The experiments included voluntary overventilation, voluntary overventilation with a large dead space, the ingestion of large amounts of sodium bicarbonate, exercise, exercise after the ingestion of sodium bicarbonate, ingestion of large amounts of ammonium chloride, and rebreathing. The effects of these procedures upon the electrocardiogram and upon the hydrogen-ion concentration, lactic acid content, and carbon-dioxide combining power of blood from the veins of the arms were investigated. In some instances the serum calcium and phosphorus were determined. Electrocardiograms and samples of venous blood were taken before and at suitable intervals following the above procedures and, when possible, as in overventilation, during the procedure.

In determining the amplitudes of the various electrocardiographic deflections, the measurements in ten successive beats were averaged and care was taken to avoid errors which might result from the effects of respiratory movements upon the curves. The standardization of each curve was recorded, and corrections were made for errors in standardization. These, however, were never great.

Overventilation.—Four subjects served for thirteen experiments in voluntary overbreathing to the point of well-developed tetany.[16] The tetany usually developed within five minutes, in one subject in three minutes, but in most of the experiments overbreathing was performed for eight to sixteen minutes, and in one instance twenty-four minutes. In all of these experiments the T-waves of Lead I became much smaller during the overbreathing, and in ten instances T of Lead II became smaller (Figs. 2, 3, and 4). In two instances T of Leads II and III became slightly taller, while in five other experiments T of Lead III became taller. In nearly all of the experiments the R-waves became smaller in Lead I and taller in Lead III. In three experiments, however, the R-waves became smaller in Lead III, and in two of these the T-waves of Lead III became taller (Table I).

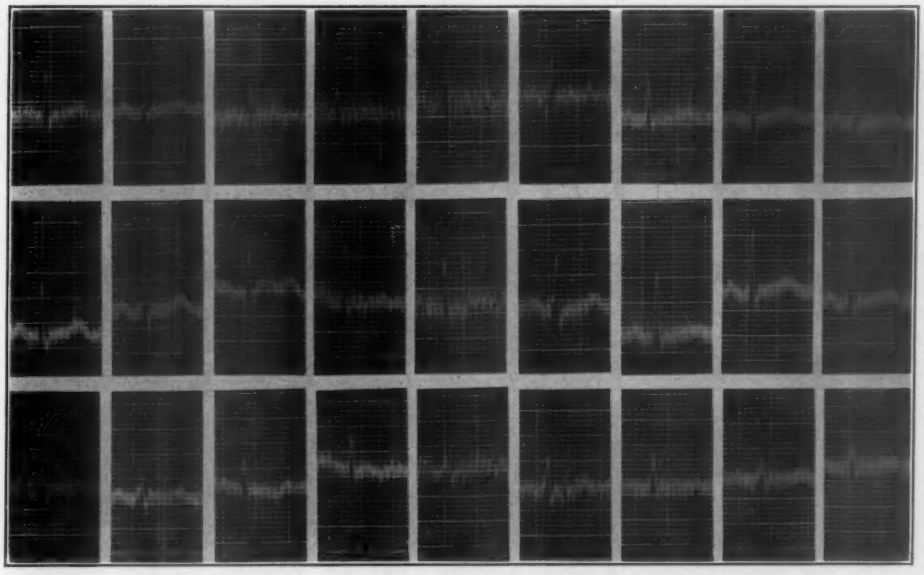

Fig. 2.—Experiment 23, subject A, voluntary overventilation for twenty-four minutes. *A*, control. *B* and *C*, during overventilation. *D*, one minute and *E*, three minutes after cessation of overventilation. *F*, *G*, and *H*, and *I* at approximately ten-minute intervals. The curves show the effects of contraction of the voluntary muscles due to tetany.

In all of these experiments tetany was produced, but in only ten experiments were blood samples taken. These showed alkalosis. The hydrogen-ion concentration of the blood from the arm veins changed from values of 7.31 to 7.38 in the control specimens to values of 7.46 to 7.65 in samples taken at the height of the tetany, or just before the overventilation was terminated. The hydrogen-ion concentration returned to normal within two to five minutes after the overbreathing was stopped. The electrocardiographic changes seemed to be related more closely to the elevation of the hydrogen-ion concentration than to other changes in

TABLE I

THE EFFECTS OF VOLUNTARY OVERVENTILATION UPON T AND R OF THE ELECTROCARDIOGRAM*

EXP. NO.	SUBJECT	BLOOD pH	T-WAVES (MILLIVOLTS)			R-WAVES (MILLIVOLTS)		
			LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
1	C	7.38 to 7.53	0.30 to 0.16 smaller	0.17 to –0.06 smaller	–0.17 to –0.22 smaller	1.40 to 0.95 smaller	1.82 to 2.14 taller	0.95 to 1.78 taller
2	D	7.36 to 7.52	0.32 to 0.19 smaller	0.38 to 0.33 smaller	0.07 to 0.14 taller	1.25 to 0.75 smaller	1.55 to 1.59 no change	0.29 to 0.50 taller
7	B		0.28 to 0.15 smaller	0.26 to 0.09 smaller	0.04 to –0.08 smaller	1.36 to 1.06 smaller	2.68 to 2.68 no change	1.59 to 2.18 taller
8	B		0.34 to 0.17 smaller	0.37 to 0.31 smaller	0.08 to 0.14 taller	1.28 to 0.99 smaller	2.19 to 2.16 no change	1.30 to 1.59 taller
9	B	7.32 to 7.50	0.31 to 0.19 smaller	0.32 to 0.12 smaller	0.05 to –0.05 smaller	0.95 to 0.77 smaller	2.22 to 1.78 smaller	1.36 to 1.86 taller
10	B	7.31 to 7.52	0.18 to 0.14 smaller	0.16 to 0.06 smaller	0.01 to –0.01 smaller	0.73 to 0.72 no change	2.05 to 1.65 smaller	1.40 to 1.77 taller
11	B	7.32 to 7.46	0.29 to 0.15 smaller	0.37 to 0.37 no change	0.08 to 0.17 taller	0.83 to 0.70 smaller	1.95 to 2.03 taller	1.12 to 1.00 smaller
20	A		0.24 to 0.04 smaller	0.16 to 0.19 taller	–0.02 to 0.09 taller	1.16 to 0.67 smaller	1.14 to 1.31 taller	0.48 to 1.07 taller
21	A	7.35 to 7.55	0.21 to 0.06 smaller	0.14 to 0.13 smaller	–0.05 to 0.05 taller	1.05 to 0.40 smaller	1.35 to 1.20 smaller	0.75 to 0.90 taller
22	A	7.31 to 7.58	0.13 to –0.01 smaller	0.06 to –0.02 smaller	–0.09 to 0.01 taller	0.52 to 0.22 smaller	1.15 to 0.72 smaller	0.78 to 0.64 smaller
23	A	7.35 to 7.65	0.10 to 0.01 smaller	0.20 to 0.00 smaller	0.08 to –0.03 smaller	0.63 to 0.59 smaller	0.93 to 0.93 no change	0.39 to 0.55 taller
24	A	7.36 to 7.55	0.11 to 0.02 smaller	0.09 to 0.09 smaller	0.00 to 0.00 smaller	0.88 to 0.32 smaller	1.26 to 0.76 smaller	0.72 to 0.55 smaller
25	A	7.35 to 7.55	0.09 to 0.00 smaller	0.09 to 0.09 taller	0.03 to 0.08 taller	0.91 to 0.71 smaller	1.19 to 1.25 no change	0.64 to 0.95 taller

*The changes in the pH of the blood, from the control to the height of the alkalosis, are shown. The figures for T and R indicate the changes from the control values to those at the height of the alkalosis. The general trend of the changes in these waves is also indicated. The data given in Tables II and III are presented similarly.

the venous blood, such as carbon-dioxide combining power, carbon-dioxide content, lactic acid content, or serum calcium or phosphorus content. There was not, however, a strict parallelism between the changes in the electrocardiograms and the changes in the hydrogen-ion concentration of the blood (Figs. 2 and 4).

In some of the experiments the electrocardiographic changes were of the type which might be caused by a change in the position of the heart, such as might occur if the diaphragm should be depressed and the heart should assume a more vertical position, causing a shift of its long axis to the right.[5] It is possible that a slight, transient emphysema of the lungs may have occurred, and that this may have been accompanied by a slight change in the position of the heart. The changes in the electrocardiograms are not, however, attributed to this alone, for the following reasons. In the first place, overventilation produced no changes in the position of the heart or diaphragm which were apparent upon physical examination. Secondly, in some of the experiments the T-wave changes were not accompanied by similar changes in the R-waves. Lastly, the observations to be described presently make such an explanation unlikely.

Voluntary overventilation removes carbon dioxide from the body in abnormally large amounts, and in this manner causes alkalosis. If, however, the atmosphere breathed is sufficiently rich in carbon dioxide, excessive removal of the gas will not occur, and alkalosis will not develop. Two subjects served for three experiments in which they voluntarily overbreathed through a large tube into a large bottle, the wide neck of which was open to the air of the room. This had the effect of increasing the dead space by about nine liters, without causing any appreciable resistance to breathing. The rate, depth, and duration (thirteen to fourteen minutes) of the overbreathing were approximately the same as in the experiments in which tetany developed. With the large dead space, however, the carbon-dioxide content of the air breathed soon reached a sufficient concentration to prevent the development of alkalosis. Samples of venous blood taken near the end of the period of overbreathing showed no change in the hydrogen-ion concentration in two experiments, and a slight change toward the acid side in one experiment, as compared with the controls. Samples of air from the dead space, taken just before the termination of overbreathing, showed carbon dioxide values of 4.8, 6.1, and 5.0 volumes per cent, and oxygen values of 18.5, 16.0, and 18.4 volumes per cent, respectively, for the three experiments. It is unfortunate that venous blood was not taken during the first few minutes of overbreathing, as it is possible that a slight degree of alkalosis may have developed at first, before the carbon dioxide of the air breathed had increased sufficiently to prevent it. One subject recognized, during the first few minutes, the tingling of the extremities which always preceded the appearance of tetany.

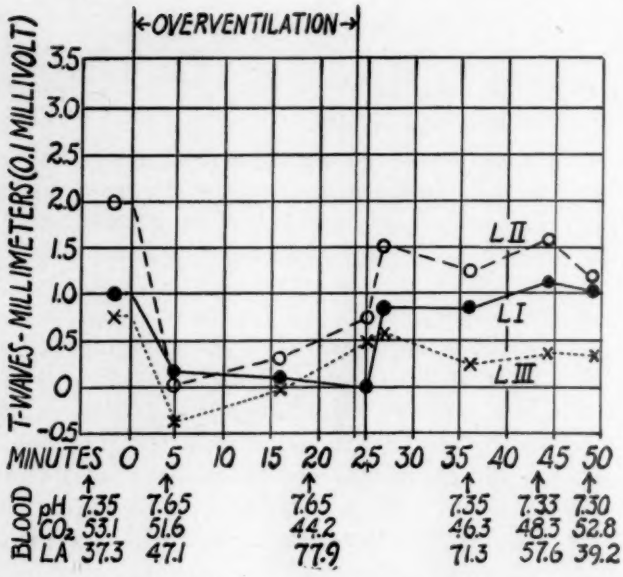

Fig. 3.—Experiment 23, subject A, showing the relation of the electrocardiographic changes to changes in the venous blood. In this and subsequent figures Lead I is represented by dots, Lead II by circles, and Lead III by crosses, while CO_2 refers to the carbon-dioxide combining power and LA to the lactic acid content of venous blood.

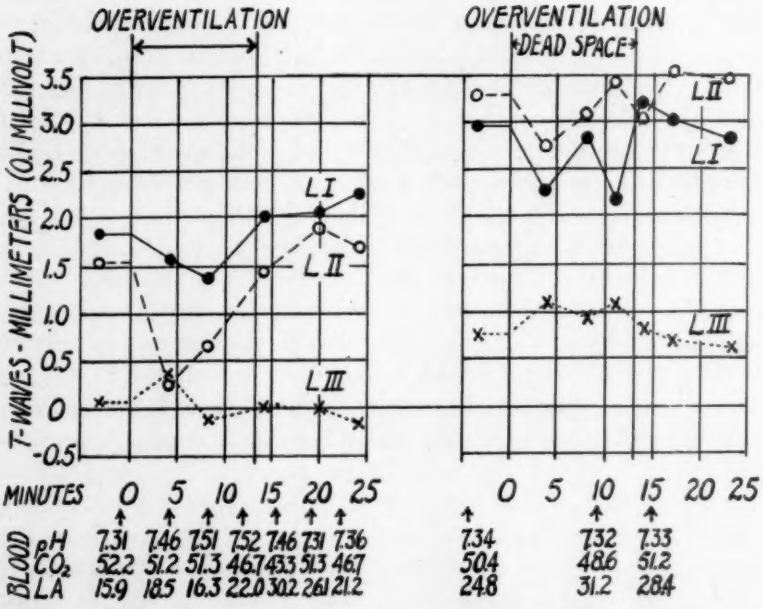

Fig. 4.—Experiment 10, subject B, voluntary overventilation, and experiment 12, subject B, voluntary overventilation with a large dead space.

The electrocardiograms showed slight changes (Figs. 3, 4, and 5). In all, the T-waves became smaller in the first few minutes of the overbreathing, only to become taller a few minutes later. In the experiment (Fig. 5) in which the reduction in amplitude of T appeared most pronounced, the T-waves of the control curve were unusually tall for this subject. The R-waves showed but slight changes, usually but not always in the same direction as the T-wave changes. In none of these experiments were the changes as pronounced or the T-waves as flattened as in the experiments in which alkalosis and tetany were produced (compare Figs. 2 and 5).

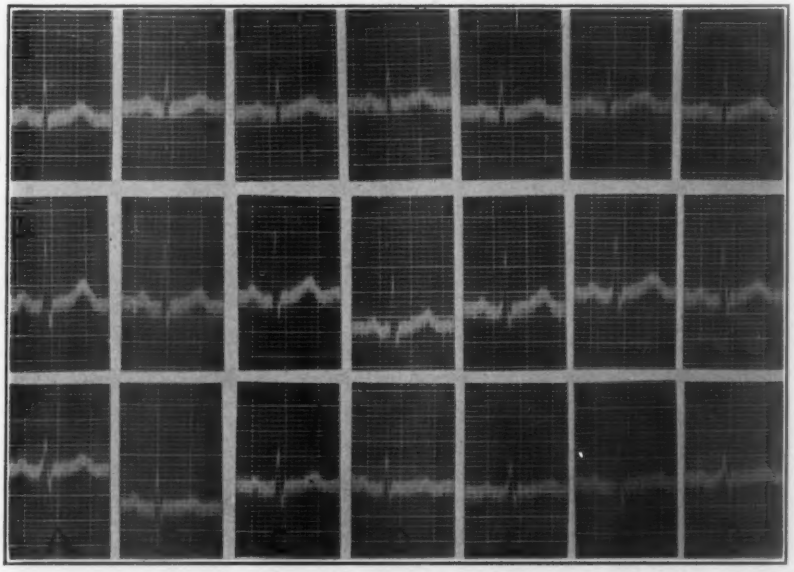

Fig. 5.—Experiment 26, subject A, voluntary overventilation with a large dead space, in which the pH and CO_2 combining power of venous blood showed no significant change. *A*, control. *B*, *C*, and *D* during overventilation. *E*, *F*, and *G* at approximately four-minute intervals following the cessation of overventilation. Compare with Fig. 2.

Sodium Bicarbonate.—In order to investigate further the question whether the electrocardiographic changes observed were related to alkalosis or to the excessive respiratory movements, four subjects served for seven experiments in which sodium bicarbonate was given by mouth in single doses of 25 to 50 gm. Moderate alkalosis was produced in all seven experiments, the hydrogen-ion concentration of the venous blood rising from values of 7.32 to 7.33 in the controls, to values of 7.48 to 7.58 at the height of the alkalosis. The carbon-dioxide combining power changed from control levels of 49.5 to 53.2 volumes per cent, to 64.6 to 74.8 volumes per cent at the height of the alkalosis. In none of these experiments did tetany occur. The hydrogen-ion concentration and carbon-dioxide combining power reached their highest values within

TABLE II

THE EFFECTS OF SODIUM BICARBONATE UPON T AND R OF THE ELECTROCARDIOGRAM

EXP. NO.	SUBJECT	BLOOD pH	T-WAVES (MILLIVOLTS)			R-WAVES (MILLIVOLTS)		
			LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
3	E	7.33 to 7.48	0.13 to 0.15 taller	0.08 to 0.16 taller	0.00 to 0.01 taller	1.08 to 1.06 no change	1.16 to 1.32 no change	0.35 to 0.30 no change
4	F	7.33 to 7.53	0.20 to 0.13 smaller	0.25 to 0.15 smaller	0.10 to 0.11 taller	1.22 to 1.10 no change	1.35 to 1.19 no change	0.60 to 0.40 no change
14	B	7.32 to 7.52	0.21 to 0.24 no change	0.15 to 0.19 no change	–0.10 to –0.07 no change	1.14 to 1.47 taller	1.92 to 1.81 no change	1.02 to 0.65 smaller
27	A		0.08 to 0.06 smaller	0.15 to 0.09 smaller	0.06 to 0.02 smaller	0.68 to 0.48 smaller	1.16 to 1.12 no change	0.40 to 0.65 taller
28	A	7.33 to 7.58	0.17 to 0.02 smaller	0.31 to 0.08 smaller	0.12 to 0.02 smaller	0.55 to 0.85 taller	0.94 to 0.80 no change	0.41 to 0.14 smaller
15*	B		0.27 to 0.13 smaller	0.27 to 0.20 smaller	0.02 to 0.06 taller	1.06 to 1.17 taller	1.76 to 1.64 no change	0.88 to 0.41 smaller
29*	A	7.34 to 7.58	0.14 to 0.13 smaller	0.19 to 0.22 smaller	0.08 to 0.08 smaller	0.83 to 0.55 no change	1.02 to 1.04 no change	0.42 to 0.37 no change

*Control observations not made; the figures for the controls are the averages of many control observations.

one to three hours after the ingestion of the sodium bicarbonate, and these values often persisted for five to nine hours. The electrocardiographic changes were usually apparent within two or three hours, and were most pronounced five or six hours after the ingestion of the sodium bicarbonate (Figs. 6 and 7).

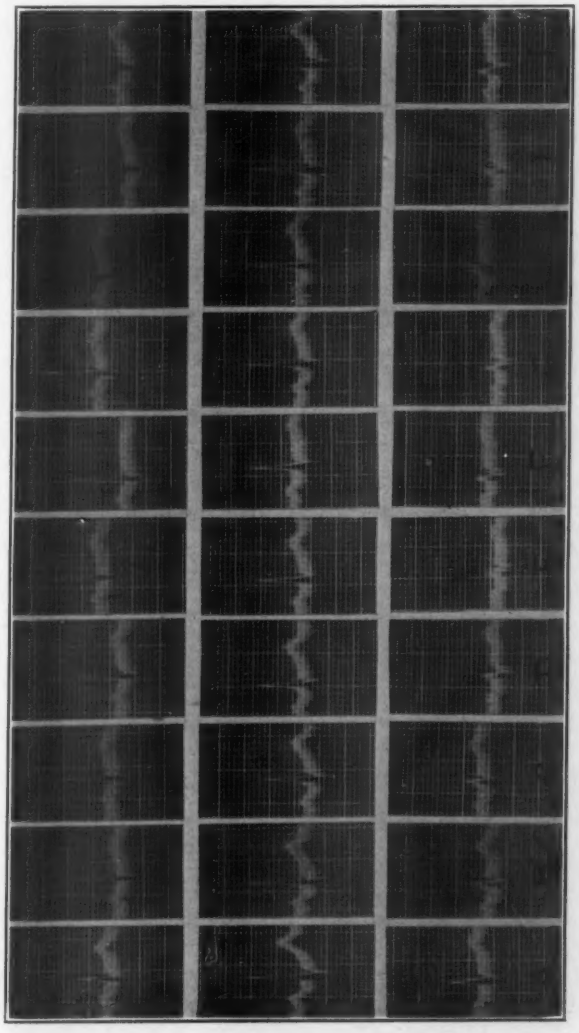

Fig. 6.—Experiment 28, subject A. *A*, control. *B* to *I*, curves taken at hourly intervals following the ingestion of 50 gm. of sodium bicarbonate. *J*, twenty-six hours later. The pH of the venous blood rose to 7.58, and the CO_2 combining power to 74.8 vol. per cent (see Fig. 7).

In five of the seven experiments with sodium bicarbonate, the alkalosis was accompanied by a definite reduction in the amplitude of the T-waves of the electrocardiograms in Leads I and II or in all three leads (Table II). In one of the experiments there were no significant changes in the T-waves, while in one experiment the T-waves became slightly taller. The R-waves usually showed no significant changes, and when they

became slightly taller or slightly smaller, these changes did not appear to be related to the T-wave changes.

The alkalosis produced by sodium bicarbonate was accompanied by a reduction in the amplitude of the T-waves. The electrocardiographic changes, however, were not directly proportional to the degree of alkalosis; the relationship was qualitative, not quantitative. This was true for both hydrogen-ion concentration and carbon-dioxide combining power.

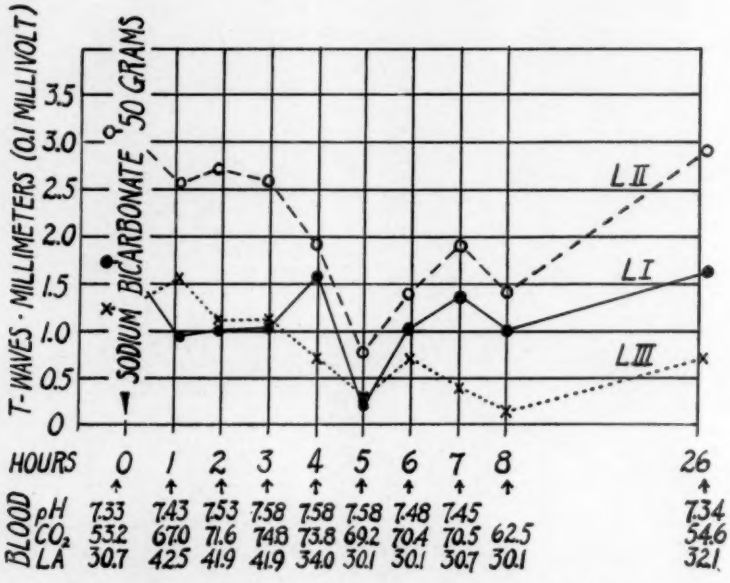

Fig. 7.—Experiment 28, subject A. Changes in the T-waves following the ingestion of 50 gm. of sodium bicarbonate.

Exercise.—Four subjects were used for one experiment each. The exercise consisted in running up and down stairs until shortness of breath and fatigue were quite pronounced. This required two and one-half to four minutes. The work performed, as estimated from the weight of the subject and the height through which he raised his weight, was 2400 to 4000 kilogram-meters. Definite acidosis was produced. The hydrogen-ion concentration of the venous blood fell to between 7.12 and 7.18, and returned to approximately normal within fifteen to thirty minutes. The carbon-dioxide combining power and lactic acid content returned to normal more gradually in about one hour, as had been observed by Barr, Himwich, and Green.[17, 18]

In the electrocardiograms the T-waves became much taller immediately after the exercise (Figs. 8 and 9), taller in all three leads in three experiments, and in Leads I and II in the other (Table III). In this last experiment T was inverted in Lead III, and became more deeply inverted after exercise. The T-waves returned to approximately normal

TABLE III

THE EFFECTS OF ACIDOSIS UPON T AND R OF THE ELECTROCARDIOGRAM

EXP. NO.	SUBJECT	BLOOD pH	T-WAVES (MILLIVOLTS)			R-WAVES (MILLIVOLTS)		
			LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
5 Exercise	F	7.33 to 7.18	0.14 to 0.17 taller	0.22 to 0.32 taller	0.09 to 0.13 taller	0.78 to 0.78 taller	0.95 to 1.22 taller	0.20 to 0.31 taller
6 Exercise	G	7.30 to 7.15	0.16 to 0.20 taller	0.09 to 0.10 taller	–0.08 to –0.10 deeper	0.80 to 0.81 taller	0.45 to 0.48 taller	–0.38 to –0.32 S less deep
16 Exercise	B		0.20 to 0.32 taller	0.11 to 0.54 taller	–0.07 to +0.23 taller	0.78 to 0.63 smaller	1.92 to 2.28 taller	1.25 to 1.74 taller
30 Exercise	A	7.33 to 7.12	0.17 to 0.19 taller	0.15 to 0.28 taller	0.06 to 0.11 taller	0.80 to 0.66 smaller	1.35 to 1.15 smaller	0.86 to 1.22 taller
4* Exercise	F	7.53 to 7.18	0.13 to 0.26 taller	0.15 to 0.48 taller	0.11 to 0.29 taller	1.10 to 1.12 no change	1.18 to 1.18 no change	0.39 to 0.70 taller
15* Exercise	B		0.13 to 0.31 taller	0.20 to 0.67 taller	0.06 to 0.31 taller	1.17 to 0.88 smaller	1.64 to 2.16 taller	0.41 to 1.11 taller
29* Exercise	A	7.58 to 7.30	0.13 to 0.27 taller	0.23 to 0.43 taller	0.08 to 0.16 taller	0.56 to 0.37 smaller	1.04 to 0.71 smaller	0.37 to 0.58 taller
17† Ammon. chlor.	B	7.33 to 7.27	0.27 to 0.27 no change	0.27 to 0.31 taller	0.02 to 0.11 taller	1.06 to 1.31 taller	1.76 to 2.48 taller	0.88 to 1.64 taller
18 Ammon. chlor.	B	7.33 to 7.30	0.28 to 0.30 taller	0.26 to 0.39 taller	0.03 to 0.07 taller	1.22 to 1.17 taller	2.13 to 2.42 taller	1.10 to 1.56 taller
31† Ammon. chlor.	A	7.34 to 7.26	0.14 to 0.18 taller	0.20 to 0.31 taller	0.08 to 0.11 taller	0.83 to 0.66 smaller	1.02 to 1.04 no change	0.42 to 0.41 no change
35 Rebreathing	A		0.12 to 0.14 taller	0.30 to 0.33 taller	0.15 to 0.20 taller	0.37 to 0.19 smaller	0.85 to 0.96 taller	0.55 to 0.77 taller

*In these experiments the exercise was undertaken during alkalosis produced by sodium bicarbonate (see text and Table II).
†Control observations not made; the figures for the controls are the averages of many control observations.

within five to ten minutes after the exercise, and in two experiments they were slightly smaller than normal from ten to fifteen minutes after the exercise, while the venous blood still showed evidence of acidosis.

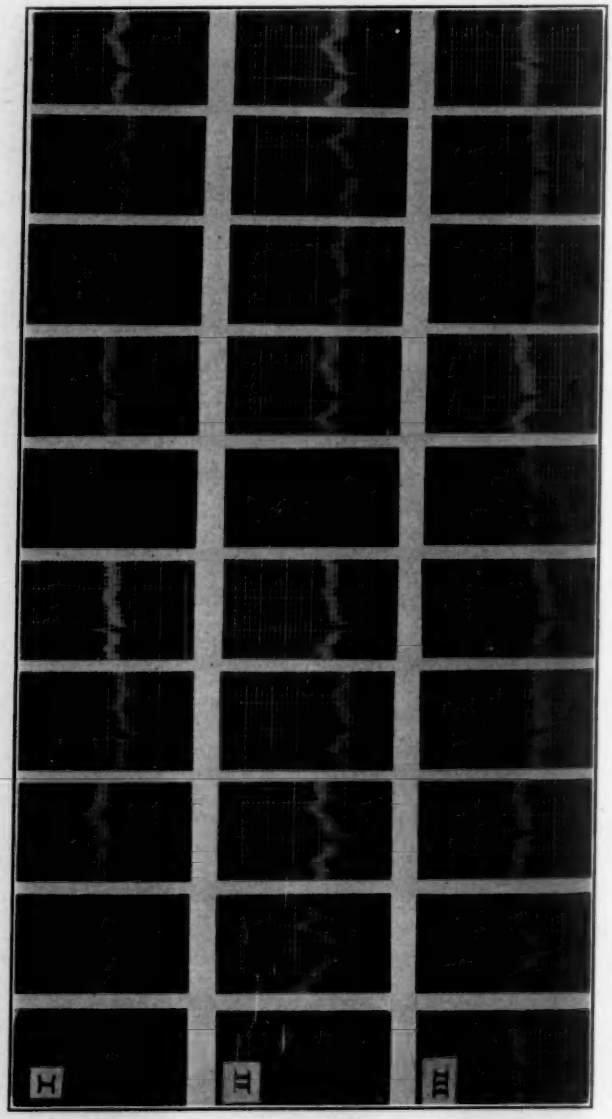

Fig. 8.—Experiment 30, subject A. *A*, control. *B* to *J*, following exercise in which approximately 4000 kilogram-meters of work were performed in four minutes (see Fig. 9).

The R-waves changed but little. They became slightly taller in Leads II and III, and in one experiment slightly smaller in Lead I. The heart rate did not return to normal for twenty to thirty minutes after the exercise.

Exercise is followed by acidosis and by a striking increase in the amplitude of the T-waves. In these experiments, also, the electro-

cardiographic changes were not directly proportional to the degree of acidosis, whether estimated by the hydrogen-ion concentration or by the carbon-dioxide combining power. The relationship was qualitative, not quantitative.

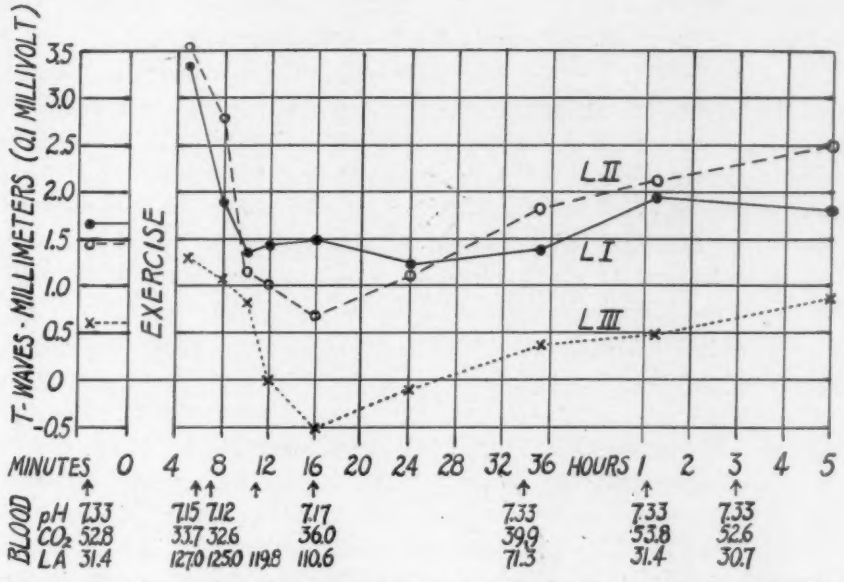

Fig. 9.—Experiment 30, subject A. T-wave changes following strenuous muscular exercise.

In three of the experiments in which sodium bicarbonate was administered the subjects exercised exactly as in the experiments just described. The exercise was performed one and one-third, three and one-fourth, and four hours, respectively, after the ingestion of the sodium bicarbonate. Alkalosis was well developed at the time of the exercise, and in two of the experiments the T-waves had become smaller. In all three experiments the T-waves of all three leads became much taller after exercise, reaching values slightly higher than after exercise alone. The R-waves did not change significantly (Table III). The hydrogen-ion concentration and carbon-dioxide combining power of the venous blood, which had shown alkalosis just before the exercise, revealed mild acidosis following the exercise. Within thirty to forty-five minutes, however, the alkalosis had returned to almost the same degree as before the exercise.

It is interesting to note that the electrocardiographic changes were not directly proportional to the degree of acidosis. Indeed, in one experiment (Exp. 29) the hydrogen-ion concentration and carbon-dioxide combining power had reached 7.58 and 74.8 volumes per cent, respectively, four hours after the ingestion of 50 gm. of sodium bicarbonate. At this point the exercise was performed and the hydrogen-ion concentration and carbon-dioxide combining power fell to only 7.30 and 36.8 volumes

per cent, respectively. In another experiment (Exp. 4), eighty minutes after the ingestion of 25 gm. of sodium bicarbonate the hydrogen-ion concentration and carbon-dioxide combining power had reached 7.53 and 74.2, respectively. At this point exercise reduced them to 7.18 and 44.3, respectively. The changes in the T-waves, however, were more pronounced in the former than in the latter experiment.

It was observed that exercise after sodium bicarbonate was followed by shortness of breath and fatigue of about the same degree as following exercise alone. Indeed, there was very little difference in these symptoms when the pH was 7.30 following exercise after sodium bicarbonate, and when the pH was 7.12 following exercise alone. In other experiments the rate and volume of respiration were determined and were found to be just as great following exercise after sodium bicarbonate as they were following exercise alone.

Ammonium Chloride.—Acidosis was produced in three experiments upon two subjects by the ingestion of single large doses of ammonium chloride (15, 20, and 25 gm.). Table III and Figs. 10 and 11 show the results. The acidosis was quite mild. In one experiment (Exp. 17) the T-waves became taller in all three leads. In the other two experiments control electrocardiograms were not obtained, but the height of the T-waves was considerably greater than their average height in a large number of control curves taken at different times for other experiments. Indeed, in one experiment the T-waves became taller than the tallest T-deflections of a large number of control curves on this subject. In the other experiment the height of T, while greater than the average, did not exceed the tallest T-waves of the various control curves on this subject. There were no significant changes in the R-waves.

Rebreathing.—In one experiment the subject rebreathed into the common type of vital capacity spirometer for five and one-half minutes. At this point the shortness of breath was unbearable. No specimens of blood were taken, but there is no doubt that a moderate acidosis was produced. The T-waves became slightly taller in all leads. The R-waves became slightly smaller in Lead I and taller in Leads II and III (Table III). The electrocardiographic changes were probably too slight to be of significance, except that the T-waves did not become smaller during excessive breathing comparable to that which produced alkalosis in the experiments upon voluntary overventilation.

The effects of atropine sulfate (1.3 mg. intravenously) and of epinephrin (0.6 mg. subcutaneously) were observed in each of two subjects. In none of these experiments did the T-waves undergo significant changes. This is of interest in that the T-waves did not become taller, as they did when the heart rate and blood pressure were increased after exercise.

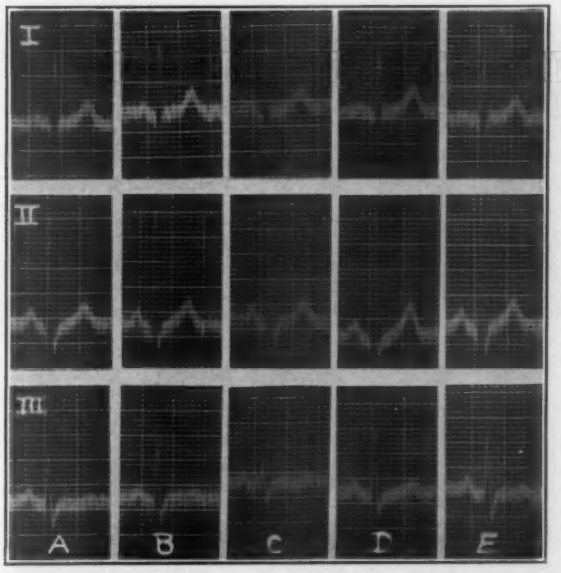

Fig. 10.—Experiment 18, subject B. *A*, control. *B*, *C*, and *D*, at intervals of approximately two hours following the ingestion of 15 gm. of ammonium chloride. *E*, twenty-four hours later. Slight acidosis was produced (see Fig. 11).

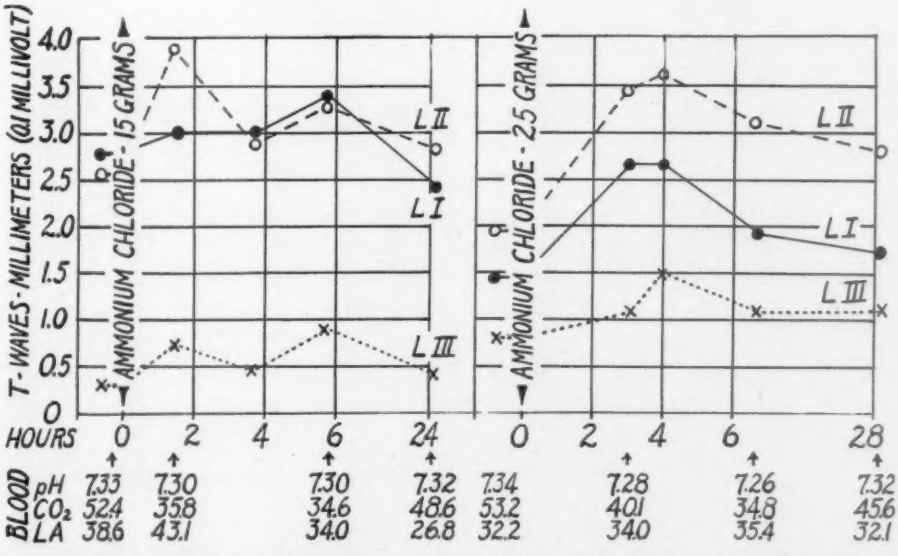

Fig. 11.—Experiment 18, subject B. Ingestion of 15 gm. of ammonium chloride. Experiment 31, subject A. Ingestion of 25 gm. of ammonium chloride. In this experiment no control observations were made. The values represented are the averages of many control observations on this subject.

Spontaneous Changes.—Two subjects served for five experiments in which they rested quietly while curves were taken at five-minute intervals. These showed slight spontaneous variations in the amplitudes of the T-waves, which, however, were not uniform in direction, and were smaller in magnitude than the changes accompanying the various experimental procedures previously described. Similarly, each subject who served for more than one experiment showed in his control curves slight variations in the amplitude of T. These, likewise, were not so pronounced as the changes induced experimentally, nor did they seem related to the slight variations in the pH or in the CO_2 combining power of the control specimens of blood.

COMMENT

While there was no direct quantitative relationship between the amplitudes of the T-waves and the degree of alkalosis or acidosis, the observations indicate that alkalosis is accompanied by a decrease and acidosis by an increase in the amplitudes of the T-waves. The results were consistent throughout the series of experiments, with only one exception. The changes in height of T were usually, but not always, more pronounced than the variations occurring spontaneously. The T-waves, however, were consistently smaller with alkalosis and taller with acidosis, and this is considered significant.

The clinical application of these observations is probably quite limited. Pronounced degrees of acidosis and alkalosis are relatively uncommon, and it is decidedly unusual to obtain electrocardiograms in such conditions. By chance, however, a curve was taken on a young woman with a normal heart who complained of palpitation shortly after the intravenous administration of sodium bicarbonate for the treatment of migraine. The curve showed strikingly inverted T-waves. On the following day the curve was normal. We have not chanced upon or recognized electrocardiographic changes which could be attributed to alkalosis or acidosis in other patients. It is not unlikely, however, that such changes may occasionally pass unrecognized.

It is not apparent why or how alkalosis and acidosis modify the electrocardiogram. The duration of systole must be altered locally, possibly to different degrees in different parts of the heart. This might be revealed by changes in the Q-T interval.

The total duration of electrical systole was determined by measuring from the beginning of the Q-R-S deflections to the end of the T-waves, and then employing the formula of Bazett,[10] which takes into account the influence of the cardiac rate: systole $= K \sqrt{\text{cycle}}$ (Table IV). During the tetany of experimental overventilation the records were too distorted by tremor to permit accurate measurements, but K was slightly increased in the patient with hysterical overbreathing, and after the ingestion of sodium bicarbonate, after exercise, after the ingestion of

ammonium chloride, and after atropine. Overbreathing into a large dead space caused no significant change in K.

In some of the experiments serum calcium determinations were made. The changes in the duration of systole were usually, but not always, inversely related to the changes in serum calcium.[11-15] When the values for K and for the serum calcium were both increased, it would seem likely that the changes in the total serum calcium value did not truly represent changes in the ionized or physiologically active calcium.[16]

TABLE IV

THE EFFECTS OF VARIOUS PROCEDURES UPON THE Q-T INTERVAL

Expressed as K of Bazett's Formula: systole $= K\sqrt{cycle}$

EXP.	SUBJECT	PROCEDURE	BEFORE	DURING*	AFTER
	Patient	Overventilation	0.343	0.384	0.370
12	B	Overventilation with dead space	0.415	0.406	0.377
13	B	Overventilation with dead space	0.389	0.400	0.402
26	A	Overventilation with dead space	0.412	0.413	0.397
35	A	Rebreathing	0.400	0.400	0.412
27	A	Sodium bicarbonate	0.428	0.437	0.411
28	A	Sodium bicarbonate	0.397	0.432	0.425
14	B	Sodium bicarbonate	0.429	0.425	----
3	E	Sodium bicarbonate	0.388	0.398	----
4	F	Sodium bicarbonate	0.394	0.436	0.382
30	A	Exercise	0.401	0.430	0.407
16	B	Exercise	0.407	0.432	0.414
5	F	Exercise	0.387	0.392	0.380
6	G	Exercise	0.394	0.404	0.401
31	A	Ammonium chloride	----	0.425	0.413
18	B	Ammonium chloride	0.380	0.388	0.400

*Curves were taken immediately after exercise.

The changes in the duration of electrical systole which we have observed were of small magnitude and of doubtful significance (Table IV). If they have any significance, they suggest that the changes in the duration of electrical systole, which must have occurred locally in the ventricles, consisted in a prolongation rather than a reduction.

SUMMARY AND CONCLUSIONS

Pronounced flattening of the T-waves was observed in a patient with hysterical overventilation and tetany. This prompted an experimental investigation of the effects of alkalosis and acidosis upon the human electrocardiogram.

Alkalosis, produced by voluntary overventilation or by the ingestion of sodium bicarbonate, is accompanied by a reduction in the amplitude of T.

Acidosis, produced by exercise or by the ingestion of ammonium chloride, is accompanied by an increase in the amplitude of T.

While the clinical application of these observations is probably quite limited, they may offer an explanation for occasional electrocardiographic changes not otherwise understood.

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STUDIES ON MERCURIAL DIURESIS

II. The Immediate Effect on the Venous Blood Pressure

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CONSIDERABLE improvement is noted by patients with heart failure following diuresis induced by the organic mercurial diuretics. Dyspnea is often noticeably ameliorated. Reduction of edema and weight loss are the most important objective evidences, although an increase in the vital capacity may also occur. We wish to point out that a reduction of the high venous blood pressure is another objective sign of betterment.

The clinical significance of the venous blood pressure has probably not obtained the attention it deserves. Lewis stresses its importance but, like Wiggers, indicates that simple inspection of the veins yields just as accurate information as direct measurement. Great discrepancies, however, are frequently found between the results obtained by inspection, and by indirect and direct methods of measurement. We believe, as does Fishberg, that the latter method has the least potentialities for inaccuracy; the principal objection to it is the necessity for venepuncture. Variations induced by changes in the degree of heart failure can be readily followed by direct measurement.

Readings of the venous pressure above the upper limit of normal indicate cardiac insufficiency in cases in which the presence of mediastinal masses and mechanical obstruction are ruled out. The high readings are pathognomonic of right-sided heart failure. As left ventricular failure is the most frequent cause of right-sided heart failure, high venous pressure then indicates left-sided insufficiency also.

Fishberg describes the systemic veins as a reservoir filled from the periphery by blood from the capillaries and emptied by the cardiac pump; normally, the intake and emptying mechanisms are in dynamic equilibrium. The venous pressure affords a measure of the filling of the reservoir. If the right side of the heart is insufficient, the reservoir fills and the venous pressure rises. If the peripheral vessels allow little blood to pass into the larger veins the level of the reservoir, and, with it, the venous pressure, falls. Many factors, cardiac and extracardiac, tend to regulate the venous pressure in the normal individual. The investigation reported in this paper was undertaken to obtain measurements, by the direct method, of the changes in venous pressure produced by mercurial diuresis in patients suffering from marked circulatory failure with pronounced edema.

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TABLE I

NO.	PATIENT	DATE	ARTERIAL BLOOD PRESSURE	VENOUS BLOOD PRESSURE	DROP IN VENOUS BLOOD PRESSURE	URINARY OUTPUT	DIURETIC
1.	T. R.	3/22	130/100	220 mm.		1400 c.c.	Esidrone 1 c.c.
		3/23	138/88	156 mm.	64 mm.	2500 c.c.	
2.	T. R.	3/26	130/86	242 mm.		1000 c.c.	Esidrone 1 c.c.
		3/27	136/94	136 mm.	106 mm.	2900 c.c.	
3.	J. S.	3/15	122/84	156 mm.		2000 c.c.	Esidrone 2 c.c.
		3/16	122/84	72 mm.	84 mm.	4000 c.c.	
4.	J. S.	3/18	118/74	125 mm.		500 c.c.	Esidrone 2 c.c.
		3/19	112/74	77 mm.	48 mm.	5000 c.c.	
5.	J. S.	3/26	132/104	228 mm.		500 c.c.	Esidrone 2 c.c.
		3/27	110/86	176 mm.	48 mm.	3200 c.c.	
6.	J. S.	3/29	118/84	142 mm.		750 c.c.	Esidrone 2 c.c.
		3/30	106/74	102 mm.	40 mm.	2500 c.c.	
7.	J. M.	3/10		162 mm.		400 c.c.	Esidrone 1 c.c.
		3/11		112 mm.	50 mm.	2200 c.c.	
8.	J. M.	3/14	212/140	80 mm.		1000 c.c.	Esidrone 1 c.c.
		3/15	146/90	70 mm.	10 mm.	1800 c.c.	
9.	J. M.	3/21	132/78	170 mm.		1300 c.c.	Esidrone 1 c.c.
		3/22	135/70	100 mm.	70 mm.	2000 c.c.	
10.	J. M.	3/26	124/78	172 mm.		500 c.c.	Esidrone 1 c.c.
		3/27	138/78	160 mm.	12 mm.	3500 c.c.	
11.	J. M.	3/29	122/70	52 mm.		2900 c.c.	Esidrone 1 c.c.
		3/30	112/68	30 mm.	22 mm.	2900 c.c.	
12.	W. S.	3/9	128/88	358 mm.		1900 c.c.	Esidrone 2 c.c.
		3/10	126/86	288 mm.	70 mm.	3000 c.c.	
13.	W. S.	3/14	125/85	410 mm.		700 c.c.	Esidrone 2 c.c.
		3/15	125/90	236 mm.	174 mm.	5000 c.c.	
14.	W. S.	3/18	110/84	315 mm.		600 c.c.	Esidrone 2 c.c.
		3/19	102/66	192 mm.	123 mm.	4400 c.c.	
15.	W. S.	3/22	128/88	154 mm.		1300 c.c.	Esidrone 2 c.c.
		3/23	128/88	80 mm.	74 mm.	3500 c.c.	
16.	W. S.	4/14		358 mm.		300 c.c.	Esidrone 1 c.c.
		4/15		300 mm.	58 mm.	2400 c.c.	
17.	W. S.	4/17		286 mm.		700 c.c.	Esidrone 1 c.c.
		4/18		274 mm.	12 mm.	2200 c.c.	
18.	W. S.	4/20		224 mm.		800 c.c.	Esidrone 2 c.c.
		4/21		166 mm.	58 mm.	2400 c.c.	
19.	W. S.	5/16		340 mm.		800 c.c.	Esidrone 1 c.c.
		5/17		212 mm.	128 mm.	5300 c.c.	
20.	W. S.	5/20		270 mm.		1100 c.c.	Esidrone 1 c.c.
		5/21		246 mm.	24 mm.	3800 c.c.	
21.	W. S.	5/25		274 mm.		1000 c.c.	Esidrone 1 c.c.
		5/26		216 mm.	58 mm.	3300 c.c.	
22.	W. S.	5/31		384 mm.		900 c.c.	Esidrone 2 c.c.
		6/1		340 mm.	44 mm.	4500 c.c.	
23.	W. S.	6/4		390 mm.		500 c.c.	Esidrone 2 c.c.
		6/5		264 mm.	126 mm.	4300 c.c.	
24.	H. D.	5/3		200 mm.		900 c.c.	Esidrone 1 c.c.
		5/4		180 mm.	20 mm.	4500 c.c.	
25.	H. D.	5/7		198 mm.		1000 c.c.	Esidrone 1 c.c.
		5/8		200 mm.	+2 mm.	3600 c.c.	
26.	H. D.	5/10		250 mm.		700 c.c.	Esidrone 1 c.c.
		5/11		176 mm.	74 mm.	2600 c.c.	

TABLE I—CONT'D

NO.	PATIENT	DATE	ARTERIAL BLOOD PRESSURE	VENOUS BLOOD PRESSURE	DROP IN VENOUS BLOOD PRESSURE	URINARY OUTPUT	DIURETIC
27.	H. D.	5/14		216 mm.		800 c.c.	Esidrone 1 c.c.
		5/15		152 mm.	64 mm.	3000 c.c.	
28.	H. D.	5/19		170 mm.		500 c.c.	Esidrone 1 c.c.
		5/20		86 mm.	84 mm.	3800 c.c.	
29.	H. D.	5/22		200 mm.		1000 c.c.	Esidrone 2 c.c.
		5/23		77 mm.	123 mm.	2000 c.c.	
30.	J. E.	4/14		160 mm.		1250 c.c.	Esidrone 1 c.c.
		4/15		140 mm.	20 mm.	2600 c.c.	
31.	J. E.	4/18		188 mm.		700 c.c.	Esidrone 1 c.c.
		4/19		128 mm.	60 mm.	1650 c.c.	
32.	B. C.	4/15		274 mm.		1000 c.c.	Esidrone 1 c.c.
		4/16		204 mm.	70 mm.	2000 c.c.	
33.	B. C.	4/18		208 mm.		700 c.c.	Esidrone 1 c.c.
		4/19		164 mm.	44 mm.	3200 c.c.	
34.	B. C.	4/21		200 mm.		500 c.c.	Esidrone 1 c.c.
		4/22		170 mm.	30 mm.	2200 c.c.	
35.	B. C.	4/28		186 mm.		600 c.c.	Esidrone 2 c.c.
		4/29		166 mm.	20 mm.	2600 c.c.	
36.	B. C.	5/3		200 mm.		400 c.c.	Esidrone 2 c.c.
		5/4		106 mm.	94 mm.	3400 c.c.	
37.	B. C.	6/24		272 mm.		500 c.c.	Esidrone 1 c.c.
		6/25		198 mm.	74 mm.	2500 c.c.	
38.	B. C.	7/11		210 mm.		800 c.c.	Esidrone 2 c.c.
		7/12		130 mm.	80 mm.	7000 c.c.	
39.	C. A.	4/26		352 mm.		100 c.c.	Esidrone 1 c.c.
		4/27		330 mm.	22 mm.	1800 c.c.	
40.	C. A.	5/2		332 mm.		1000 c.c.	Esidrone 1 c.c.
		5/3		240 mm.	90 mm.	4000 c.c.	
41.	C. A.	5/6		350 mm.		1000 c.c.	Esidrone 1 c.c.
		5/7		182 mm.	168 mm.	4000 c.c.	
42.	C. A.	5/10		172 mm.		800 c.c.	Esidrone 1 c.c.
		5/11		116 mm.	56 mm.	4000 c.c.	
43.	C. A.	6/5		248 mm.		800 c.c.	Esidrone 1 c.c.
		6/6		164 mm.	84 mm.	4000 c.c.	
44.	T. P.	4/24		315 mm.		600 c.c.	Esidrone 1 c.c.
		4/25		176 mm.	139 mm.	5800 c.c.	
45.	T. P.	4/30		254 mm.		1000 c.c.	Esidrone 1 c.c.
		5/1		120 mm.	134 mm.	3000 c.c.	
46.	F. M.	4/21		266 mm.		200 c.c.	Esidrone 1 c.c.
		4/22		226 mm.	40 mm.	4000 c.c.	
47.	F. M.	7/5		330 mm.		700 c.c.	Esidrone 1 c.c.
		7/6		240 mm.	90 mm.	4900 c.c.	
48.	A. F.	4/19		320 mm.		500 c.c.	Esidrone 2 c.c.
		4/20		276 mm.	44 mm.	5300 c.c.	
49.	A. F.	4/21		310 mm.		800 c.c.	Esidrone 2 c.c.
		4/22		296 mm.	14 mm.	4000 c.c.	
50.	A. F.	4/25		364 mm.		1800 c.c.	Esidrone 2 c.c.
		4/26		306 mm.	58 mm.	4000 c.c.	
51.	A. F.	4/29		330 mm.		1100 c.c.	Esidrone 2 c.c.
		4/30		248 mm.	82 mm.	5300 c.c.	
52.	A. F.	5/7		300 mm.		1200 c.c.	Esidrone 2 c.c.
		5/6		176 mm.	124 mm.	8300 c.c.	

TABLE I—CONT'D

NO.	PATIENT	DATE	ARTERIAL BLOOD PRESSURE	VENOUS BLOOD PRESSURE	DROP IN VENOUS BLOOD PRESSURE	URINARY OUTPUT	DIURETIC
53.	A. F.	5/16		270 mm.		1000 c.c.	Esidrone 1 c.c.
		5/17		226 mm.	44 mm.	1800 c.c.	
54.	A. F.	5/20		274 mm.		700 c.c.	Esidrone 2 c.c.
		5/21		220 mm.	54 mm.	1900 c.c.	
55.	A. F.	5/27		278 mm.		300 c.c.	Esidrone 1 c.c.
		5/28		216 mm.	62 mm.	3500 c.c.	
56.	A. F.	5/31		274 mm.		300 c.c.	Esidrone 2 c.c.
		6/1		250 mm.	24 mm.	3000 c.c.	
57.	A. F.	6/15		286 mm.		1500 c.c.	Esidrone 2 c.c.
		6/16		194 mm.	92 mm.	5700 c.c.	
58.	A. F.	6/20		208 mm.		1300 c.c.	Esidrone 2 c.c.
		6/21		160 mm.	48 mm.	6000 c.c.	
59.	A. F.	6/27		156 mm.		1200 c.c.	Esidrone 2 c.c.
		6/28		92 mm.	64 mm.	4600 c.c.	
60.	A. F.	7/1		128 mm.		1200 c.c.	Esidrone 2 c.c.
		7/2		98 mm.	30 mm.	4600 c.c.	
61.	A. S.	6/22		274 mm.		400 c.c.	Esidrone 1 c.c.
		6/23		272 mm.	32 mm.	2200 c.c.	
62.	A. S.	6/27		330 mm.		200 c.c.	Esidrone 1 c.c.
		6/28		250 mm.	80 mm.	2600 c.c.	
63.	A. S.	7/5		288 mm.		700 c.c.	Esidrone 1 c.c.
		7/6		204 mm.	84 mm.	2000 c.c.	
64.	J. T.	5/5		170 mm.		650 c.c.	Esidrone 1 c.c.
		5/6		88 mm.	82 mm.	3200 c.c.	
65.	J. T.	6/5		232 mm.		400 c.c.	Esidrone 1 c.c.
		6/6		170 mm.	62 mm.	1000 c.c.	
66.	J. T.	6/15		140 mm.		50 c.c.	Esidrone 1 c.c.
		6/16		118 mm.	22 mm.	1400 c.c.	
67.	F. B.	4/22		266 mm.		200 c.c.	Esidrone 1 c.c.
		4/23		76 mm.	190 mm.	3300 c.c.	
68.	W. L.	4/17		256 mm.		600 c.c.	Esidrone 1 c.c.
		4/18		126 mm.	130 mm.	4000 c.c.	
69.	F. L.	4/15		220 mm.		1600 c.c.	Esidrone 1 c.c.
		4/16		74 mm.	146 mm.	3500 c.c.	
70.	C. S.	4/26		302 mm.		800 c.c.	Esidrone 1 c.c.
		4/27		148 mm.	154 mm.	4000 c.c.	
71.	J. S.	4/15		220 mm.		1900 c.c.	Esidrone 2 c.c.
		4/16		104 mm.	116 mm.	2800 c.c.	
72.	J. H.	5/16		74 mm.		900 c.c.	Esidrone 1 c.c.
		5/17		40 mm.	34 mm.	1900 c.c.	
73.	J. S.	5/16		244 mm.		1300 c.c.	Esidrone 1 c.c.
		5/17		150 mm.	94 mm.	4500 c.c.	
74.	J. C.	5/27		112 mm.		2000 c.c.	Esidrone 1 c.c.
		5/28		76 mm.	36 mm.	3500 c.c.	
75.	N. H.	5/16		94 mm.		900 c.c.	Esidrone 1 c.c.
		5/17		72 mm.	22 mm.	1900 c.c.	
76.	W. H.	5/16		90 mm.		400 c.c.	Esidrone 1 c.c.
		5/17		70 mm.	20 mm.	1900 c.c.	
77.	F. C.	6/11		84 mm.		500 c.c.	Esidrone 1 c.c.
		6/12		64 mm.	20 mm.	2000 c.c.	
78.	C. F.	6/22		130 mm.		400 c.c.	Esidrone 1 c.c.
		6/23		90 mm.	40 mm.	1500 c.c.	
79.	W. L.	7/6		254 mm.		1700 c.c.	Esidrone 1 c.c.
		7/7		100 mm.	154 mm.	5000 c.c.	

METHOD OF STUDY

The direct manometric method, using an 18-gauge needle in the antecubital vein, was employed, with 3 per cent sodium citrate solution as the anticoagulant. The arm position recommended by Griffith, Chamberlin and Kitchell in their modification of the Moritz and Tabora technique was selected. The normal variations of venous pressure by this method range between 60 and 120 mm. of water. We recognize the difficulty in making precise correction for the zero reference point, but believe that the level of the auricle can be readily estimated for the hydrostatic pressure equilibration. However, adduction of the arm was not complete, and slight flexion, in supination, at the elbow was permitted, thus obviating the objections raised by Brandt and Katz.

All patients studied were placed on our cardiac regime, consisting of rest in bed and a diet of 1683 calories (carbohydrate 215 gm., protein 55 gm., fat 67 gm., sodium chloride 0.985 gm.) with a total twenty-four-hour fluid intake of 1600 c.c., including the calculated water content of foods. Potassium chloride was given at meals. Digitalis and ammonium chloride were used in most of the cases, with morphine and phenobarbital when necessary. A control period of three days generally preceded the initiation of mercurial diuresis. The weight and twenty-four-hour urinary output were recorded daily. The venous blood pressure was measured by the direct method on admission, three days later, before the injection of the mercurial diuretic, and again twenty-four hours later. All readings were made at the same hour in the morning. Subsequent determinations were made before, and twenty-four hours following, the administration of the diuretic. The diuretic employed was esidrone (Ciba), the sodium salt of pyridinedicarboxy-β-mercuri-ω hydroxypropylamide-theophylline, which contains 31.2 per cent of mercury in nonionizable form and 28 per cent of theophylline which is bound chemically to the mercury molecule. It is a stable, neutral, crystalline substance which is readily soluble in water. We have reported the remarkable effectiveness of esidrone in a previous communication. In this study esidrone was administered intravenously in doses of 1 or 2 c.c.; each cubic centimeter contains 0.14 gm. of the drug, which equals 0.043 gm. of mercury.

Table I summarizes the venous blood pressure readings in seventy-nine patients before, and twenty-four hours after, the intravenous injection of esidrone. The highest pressure in the series was 410 mm. The maximum drop in twenty-four hours following administration of the diuretic was 174 mm. (from 410 mm. to 236 mm.). The average drop was 70 mm. One patient showed a rise of 2 mm. despite an output of 3600 c.c. In all of the others there was a decrease, as Table I demonstrates. It is to be remarked that all of the patients had pronounced edema, which accounts for the large outputs. Included in the group were cases of hypertensive and arteriosclerotic, rheumatic, syphilitic, and thyrotoxic, heart disease, and chronic cor pulmonale.

DISCUSSION

We have found very little variation in the abnormal venous blood pressure readings in edematous patients unless pronounced diuresis occurs. The following examples (Table II) illustrate this point.

TABLE II

	URINARY OUTPUT	VENOUS BLOOD PRESSURE	COMMENT
F. M.			
7/ 3/38	300 c.c.	296 mm.	
7/ 4/38	200 c.c.	346 mm.	
7/ 5/38	300 c.c.	330 mm.	
7/ 6/38	4900 c.c.	240 mm.	Esidrone 1 c.c.
W. M.			
7/ 2/38	700 c.c.	366 mm.	
7/ 3/38	860 c.c.	336 mm.	
7/ 4/38	580 c.c.	330 mm.	
7/ 5/38	1800 c.c.	260 mm.	Spontaneous diuresis
7/ 6/38	1700 c.c.	254 mm.	Spontaneous diuresis
7/ 7/38	5000 c.c.	100 mm.	Esidrone 1 c.c.
E. A.			
7/22/38	600 c.c.	330 mm.	
7/23/38	1000 c.c.	320 mm.	
7/24/38	700 c.c.	340 mm.	

It will be observed that diuresis is associated with the drop in venous blood pressure, and that the fall is directly proportional to the degree of diuresis. When relatively slight spontaneous diuresis occurs the drop in the venous pressure is relatively small, whereas with the pronounced diuresis produced by esidrone the drop in the venous blood pressure is much more pronounced. A large spontaneous diuresis naturally produces the same result. These statements apply to the immediate effects at the end of twenty-four hours. In cases in which improvement continued as a result of general cardiac management and repeated injections of the diuretic, the venous blood pressure continued to descend until it reached normal values. However, a rise generally occurred after the diuresis subsided, although the previous high levels were not attained unless the edema became more pronounced or the heart failure more severe.

These observations indicate that the venous blood pressure falls as diuresis occurs. The cause of the decrease may be ascribed to one or several factors. The pressure of edema fluid surrounding the peripheral veins decreases with diuresis, thus increasing the capacity of the veins. This lowers the venous blood pressure by permitting relaxation. Second, it may be that the heart muscle itself is edematous; if so, a reduction of this edema should increase its efficiency. Third, the increase in vital capacity which follows the diuresis means that intrathoracic pressure is more negative, with the result that blood flow into the thorax is facilitated. Again, the reduction of edema in and about the peripheral muscles improves the efficiency of muscle contraction, which is an important factor in venous flow. In another communication we shall present evidence to indicate that diuresis influences the central nervous system, and therefore the central venopressor regulating mechanism.

SUMMARY AND CONCLUSIONS

The immediate effect of mercurial diuresis (and also of copious spontaneous diuresis) on the venous blood pressure is to produce a decrease. The drop in venous pressure is apparently directly proportional to the degree of diuresis. This fall in venous pressure is an objective measure of clinical improvement in the treatment by mercurial diuretics of patients with heart failure and edema.

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PLETHYSMOGRAPHIC STUDIES OF PERIPHERAL BLOOD FLOW IN MAN

I. Criteria for Obtaining Accurate Plethysmographic Data*

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THE problem of blood flow in the extremities under various physiologic and pathologic states has recently been subjected to further investigation. The studies generally have employed the plethysmograph, although occasionally the indirect calorimetric method[1, 2] has been substituted. With the latter, the extremity is immersed in a known volume of water and the amount of heat given off in a definite period of time is measured by noting the increase in the temperature of the water. With the former method, the extremity is inserted into a plethysmograph and the initial rate of swelling of the limb recorded when a collecting pressure is applied, i.e., one sufficient to occlude venous outflow without interfering with arterial inflow. The principle underlying this procedure was utilized by Brodie[3] for determining blood flow through an organ, and was then modified by Hewlett and van Zwaluwenburg[4] for similar measurements in an extremity. The method was not widely employed until recently, when Freeman[5] modified it somewhat to measure blood flow in the hand. Numerous investigators have made use of the hand plethysmograph in various physiologic experiments,[6-9] while others have worked with a similar type of apparatus for measuring blood flow through the forearm[10-12] and the foot.[6, 12]

Critical perusal of the pertinent literature reveals a marked variation in the absolute blood flow figures for apparently normal subjects. In fact, great differences have been observed in the same individual on different days, a finding which is probably due in part to normal variations in cardiac output. Most investigators either state or imply that conditions must be controlled rigidly if any significance is to be attached to such results. However, these conditions and the manner of controlling them are generally only casually mentioned, or not in sufficient detail to be of help in guiding a beginner in the field.

Since interest in peripheral vascular disease continues to increase, and since the method of choice in the study of this subject will most likely

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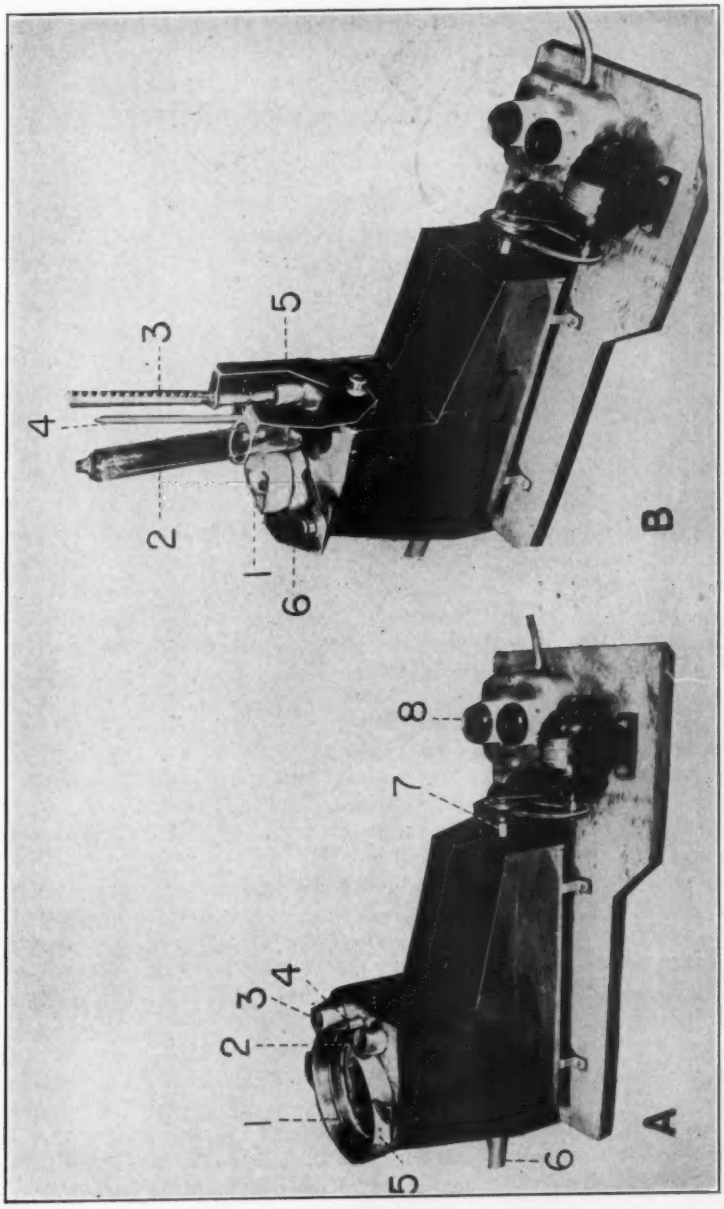

Fig. 1.—Photographs of foot plethysmograph. *A, 1,* Edge of inner cylinder over which rubber membrane is stretched and held in place with brass ring; *2,* opening for wide glass tube; *3,* opening for calibrating burette; *4,* opening for thermometer; *5,* support for iris diaphragm; *6,* outlet tube for removal of water; *7,* shaft of propeller for stirring water; *8,* switches for propeller and electric heater. *B, 1,* Rubber cuff attached to rubber membrane; *2,* wide glass tube; *3,* calibrating burette; *4,* thermometer; *5,* support for glass tube and burette; *6,* iris diaphragm covering rubber diaphragm, held in place by thumb screw.

involve the further use of the plethysmograph, it was considered advisable to investigate in detail the various mechanical and physical difficulties which must be overcome before constant and reliable blood flow data can be obtained. The purpose of the present report is to describe those conditions which may lead to the production of artifacts, and the means utilized to correct or eliminate them. In all instances, blood flow figures for the foot were obtained simultaneously with those for either the hand or forearm.

DESCRIPTION OF PLETHYSMOGRAPHS AND OF PRELIMINARY PREPARATION FOR BLOOD FLOW DETERMINATIONS

Foot Plethysmograph.—The foot plethysmograph (Fig. 1) consists of two containers of brass or monel metal (one fitted into the other so as to form an insulated space) which are made grossly in the shape of a boot and sufficiently large to permit easy entrance of the foot. The latter is inserted into the machine for a distance of 8½ inches and rests on a fine wire mesh placed about 1½ inches from the bottom of the inner chamber. Below this platform are an electric stirrer and an electric heater. At the upper end, besides the aperture through which the foot passes, there are three other openings for a thermometer, wide glass tube, and calibrating burette, respectively (Fig. 1*A: 4, 2, 3*).

A cuff, made from the wrist portion of a surgical glove and connected to a diaphragm of heavy rubber (one-sixty-fourths of an inch in thickness), is attached snugly to the skin of the leg with rubber cement, and the foot is then inserted into the plethysmograph, previously two-thirds filled with water at 32° C. The upper end of the apparatus is made water-tight by stretching the membrane over the edge of the inner cylinder (Fig. 1*A: 1*) and clamping it in place with a brass ring. In order to prevent bulging of the rubber, a felt pad, cut out to conform to the leg, is placed above the rubber membrane and held in position with an iris diaphragm (Fig. 1*B: 6*). Water is added until the apparatus is filled completely, and then the thermometer, wide glass tube, and calibrating burette are placed in the three openings at the upper end of the machine (Fig. 1*B: 4, 2, 3*). All air is expelled and water from the burette permitted to enter until a level is observed in the glass tube. The burette is then clamped off and the glass tube connected with rubber tubing to a Brodie's bellows* of 20 c.c. capacity. A modified sphygmomanometer cuff, 2 inches wide, is placed around the leg and connected to a reservoir and mercury manometer which are so arranged that the cuff can be inflated to the desired pressure, and deflated, without any lag.

Forearm Plethysmograph.—In the case of the forearm plethysmograph, the procedure is a little more time-consuming, for, since the hand is excluded from the interior of the recording chamber, there are two openings, i.e., the entrance to, and the exit from, the apparatus, which must be made water-tight. In order to minimize vasomotor responses, it has been thought desirable to immerse the hand in water at the same temperature as that surrounding the forearm. The plethysmograph (Fig. 2), therefore, consists of an inner brass cone, the recording chamber, which is 5½ inches long (having a diameter of 5¼ inches at one end, and 4½ inches at the other) and contains three holes on its upper surface for the insertion of a thermometer, wide glass tube, and calibrating burette (Fig. 2*B: 5, 3, 4*). The inner cone is suspended permanently at its larger end in a brass receptacle (Fig. 2*C*). Rubber

*Recently Freeman and Zeller[13] have suggested the use of a miniature Krogh spirometer, which evidently has certain advantages over the Brodie's bellows for recording blood flow measurements.

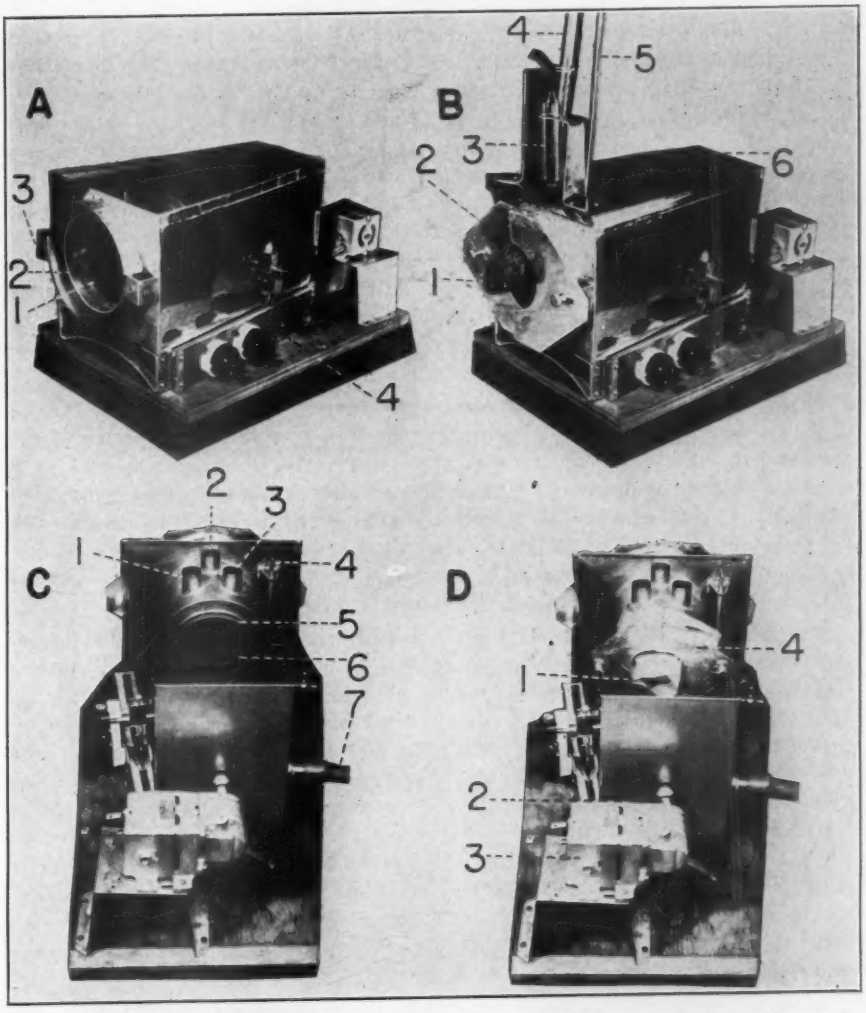

Fig. 2.—Photographs of forearm plethysmograph. *A*, View showing entrance to apparatus; *1*, wire screen for support of forearm; *2*, edge of inner cylinder over which rubber membrane is stretched and held in place with brass ring; *3*, support for iris diaphragm; *4*, panel board with switches for electric heater and propeller. Above it is a thermostat. *B*, Same view with rubber membrane stretched over ring and supported by iris diaphragm; *1*, rubber cuff attached to rubber diaphragm; *2*, iris diaphragm in position; *3*, large glass tube; *4*, calibrating burette; *5*, thermometer; *6*, lid covering outer chamber. *C*, View showing interior of plethysmograph; *1*, opening for thermometer; *2*, opening for large glass tube; *3*, opening for calibrating burette; *4*, outlet tube for inner chamber; *5*, edge of inner cylinder over which rubber membrane is stretched and held in place with brass ring; *6*, wire screen, same as *A*, *1*; *7*, outlet tube for outer chamber. *D*, Same view as *C* except that rubber membrane is stretched over exit to plethysmograph; *1*, rubber cuff attached to rubber membrane; *2*, shaft of propeller for stirring water; *3*, electric motor; *4*, iris diaphragm in place.

In order to convert apparatus into a hand plethysmograph, a piece of rubber sheeting is substituted for membrane with cuff attached, and this is stretched over the exit to inner chamber and supported by a wooden disc and iris diaphragm.

cuffs (each connected to a rubber diaphragm) are attached with rubber cement to the proximal and distal portions of the forearm, which is then inserted into the plethysmograph so that the hand passes through to rest on a support in the outer chamber. Both openings to the plethysmograph are made water-tight by stretching the diaphragms attached to the cuffs over the ends of the inner tube (Fig. 2*A: 2* and *C: 5*) and retaining them in place with rings; the membranes are prevented from bulging as in the foot apparatus (Fig. 2*B: 2* and *D: 4*). The inner and outer chambers are then filled with water at 32° C., all air is excluded from the former, and the thermometer, large glass tube, and calibrating burette are inserted into their respective openings (Fig. 2*B: 5, 3, 4* and *C: 1, 2, 3*); the glass tube is connected by pressure tubing to a Brodie's bellows of 20 c.c. capacity. The temperature of the water in the inner and outer chambers is kept at the desired level by means of an electric heater immersed in the water, and an electric stirrer situated in the outer chamber. A lid (Fig. 2*B: 6*) placed over the latter diminishes the loss of heat to the outside. A blood pressure cuff, about 2 inches in width, is placed around the arm and connected to a pressure reservoir.

Hand Plethysmograph.—The forearm plethysmograph, described above, can be used to obtain blood flow in the hand alone by closing off the inner opening of the recording chamber (Fig. 2*C: 5*) with a piece of rubber sheeting supported by a wooden disk and iris diaphragm.* This forms a compartment large enough to contain the hand comfortably. All steps for preparing and enclosing the extremity in the plethysmograph are similar to those described above. The modified sphygmomanometer cuff (about 1½ inches wide), however, is applied to the lower portion of the forearm close to the entrance of the extremity into the plethysmograph.

The subject of the experiment lies comfortably relaxed on a couch with the extremities (generally the contralateral upper and lower ones) in their respective machines. In using the lower plethysmograph, which is raised somewhat from the floor, the thigh is slightly extended over the couch with the leg almost at right angles to the rest of the body, so as to permit the foot to rest comfortably on the wire mesh platform. Care is taken to remove any strain on the hamstrings. In using the hand or forearm plethysmograph, the upper extremity lies at about the level of the heart, making an acute angle with the trunk. The arm is supported and held firmly in place by means of sand bags, but care is taken not to exert any pressure on the superficial veins. The subject is lightly clothed and the environmental temperature is maintained as constant as possible between the limits of 25 and 27° C. All external stimuli, as well as emotional distractions, are excluded so as to reduce nervousness and apprehension to a minimum.

Since the preparations associated with the above procedures consume more than one-half hour, the subject has an opportunity to rest for at least this period of time before determinations of blood flow are made. When all preliminary work is completed, each Brodie's bellows is half filled with air and connected to a small aluminum cup-pen by a long light lever; the pens and an electric time marker, recording seconds, are then aligned on the drum. Following this, the venous pressure is measured in order to determine the degree of obstruction to the superficial veins. This is obtained by observing the lowest pressure in the cuff which causes an increase in the size of the extremity. In the hand or forearm it is generally less than 10 mm. Hg, while in the foot it is about 35 mm. Hg. Blood flow measurements are then obtained by simultaneously producing an occlusion pressure of 70 mm. Hg in the upper cuff and 110 mm. Hg in the one on the leg, maintaining it for a period of about ten seconds, and recording the initial rate of increase in the volume of each

*In some experiments the hand plethysmograph described by Freeman[5] was used.

extremity. The pressures are then released and a tracing obtained of the return to the baseline. In the case of the forearm, Grant and Pearson[12] have recently presented evidence to show that it is necessary to place another blood pressure cuff around the lower portion of the extremity, close to its emergence from the plethysmograph. A pressure of 200 mm. Hg is applied fifteen seconds before, and maintained during, the period of blood flow determination. If this procedure is not followed, the rate of swelling of the portion of the forearm in the plethysmograph will be influenced by venous return from the part lying distally to it. Blood flow measurements are recorded at frequent intervals, but are never repeated within a period of time equal to twice the duration of the preceding period of application of pressure.

DISCUSSION OF METHOD

The above method may be open to criticism because of the many factors, some beyond control, which can change blood flow markedly. Therefore, in order to be able to attach significance to data thus obtained, it is essential first to present in detail the conditions under which they are collected and the precautions taken to minimize the variables.

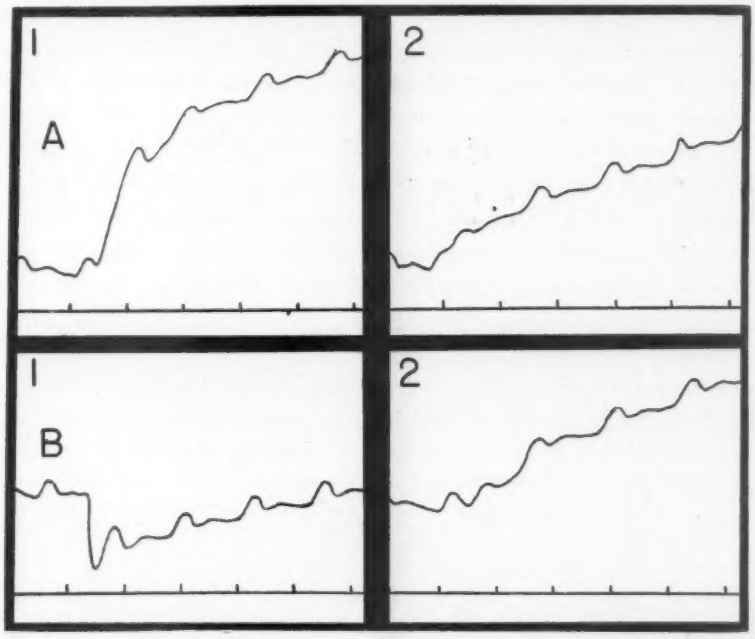

Fig. 3.—Examples of artifacts in records. *A, 1,* Artifact in a record representing blood flow in the foot, produced by the movement inward of the extremity upon production of occlusion pressure in the modified sphygmomanometer cuff; *2,* artifact eliminated from record by readjustment of cuff. *B, 1,* Artifact in a record representing blood flow in the foot, produced by the movement outward of the extremity upon production of occlusion pressure; *2,* artifact eliminated from record by readjustment of cuff.

Position of Sphygmomanometer Cuff.—It was found that the position of the blood pressure cuff was important in obtaining accurate readings. When applied incorrectly, it tended to produce artifacts by causing the extremity to move in or out of the plethysmograph as the pressure was let into the bag. A movement inward was easily identified by an almost

abrupt ascent of the lever and then a sudden change in the contour of the curve, which became more gradual in its rise (Fig. 3*A: 1*). A movement outward of the extremity generally produced a sudden drop in baseline, followed by a more gradual rise (Fig. 3*B: 1*). When these artifacts were observed on the drum, the position of the cuff was changed until they disappeared.

In reference to the procedure of obtaining measurements of blood flow through the hand, it was found that varying the position of the blood pressure cuff did not (except in occasional instances) alter the results so long as it remained upon the forearm. For the sake of uniformity, however, the cuff was placed around the wrist about one-half inch behind the iris diaphragm. With the forearm plethysmograph, a satisfactory position for the cuff was generally obtained by wrapping it around the lower portion of the arm, just above the elbow. In the lower extremity, it was found advantageous to place the cuff around the flattest portion of the calf, about 4 inches above the point of entrance of the leg into the plethysmograph, since the possibility of producing artifacts was less with this position than with any other one. Actually, a satisfactory application of the cuff was generally obtained only after a number of trials, and in some subjects with well-developed, bulging calf muscles it was impossible to find a position which did not result in the production of artifacts in the records.

Occlusion Pressure.—In respect to the pressures necessary to occlude veins without interfering with arterial inflow, it was found that although pressures as low as 40 mm. Hg were satisfactory for the upper extremity, with 70 mm. the effect was always maximal. Pressures above this level tended to decrease the abruptness of the ascent of the curve. In the case of the foot, it was necessary to raise the pressure to 110 mm. before consistently maximal flows were obtained, although pressures as low as 80 mm. sometimes produced similar results.

Position of Lower Plethysmograph.—As has been stated before, it was found that the constrictive effect of the glove upon the superficial veins of the upper extremity was so slight that the resulting venous pressure was generally less than 10 mm. Hg. However, in the case of the foot, although the cuff was applied with equal care, the apparent venous pressure, as measured by the method described above, was generally 35 to 40 mm. Hg. This high pressure was thought to be due to the fact that the leg was in the dependent position during the test, and also to the fact that a certain amount of the pressure applied to the leg was dissipated in compressing a greater proportion of muscle tissue (as compared with the forearm and arm) before it could effectively occlude the veins and thus increase the volume of the extremity; the latter was the criterion for determining venous pressure. In reference to the first

point, in a number of trials the lower extremity was extended horizontal to the body and the plethysmograph fitted over it in this position, whereupon it was found that practically the same minimal pressure was necessary to produce an increase in the foot-leg volume. Besides, it was soon realized that this position was impracticable, since it was conducive to the formation of leaks between the cuff and the leg because the hydrostatic pressure of the water in the plethysmograph (equal to about 25 mm. Hg) tended to peel the adherent glove away from the skin. Consequently this position was utilized only occasionally.

Air in Apparatus.—A number of previous investigators[5, 7, 9, 13] advocated filling the plethysmograph completely with water and then removing a certain amount (10 to 50 c.c.) so that there would be a thin layer of air in the apparatus for transmission of volume changes to the Brodie's bellows. This method was tried at the beginning, but was soon found unsatisfactory for a number of reasons. First of all, there was a tendency to the formation of isolated air pockets not connected with the main body of air. These pockets acted as cushions which tended to be compressed during a blood flow determination and, as a result, the full extent of the volume change of the extremity was not recorded on the drum. Furthermore, slight movements of the hand in or out of the apparatus would vary the relative amounts of air and water present. An attempt was made to overcome this difficulty by filling the machine entirely with water before each determination, and then removing the desired amount. This was a rather tedious and time-consuming procedure and did not do away with the possibility of formation of air pockets. Another objection to the use of air in the plethysmograph was the fact that the temperature of the room was generally lower than that of the water and, as a result, the air in the plethysmograph was exposed to a temperature which was greater than that in the Brodie's bellows (which might be considered to be grossly equal to that of the room). Consequently, as the air in the plethysmograph was heated, it expanded and left the machine, and cool air replaced it, thus causing spontaneous artifacts in the baseline. This factor was especially troublesome when the temperature of the plethysmograph was raised to 45° C. while that of the room remained at 25° C.

In order to overcome the above difficulties the plethysmograph was filled entirely with water and all air pockets were dislodged by tilting the apparatus a number of times; with each attempt water was permitted to enter from the calibrating burette. When no more air could be expelled the amount of water in the plethysmograph was increased until it could be seen in the wide glass tube leading to the Brodie's bellows. It was maintained at this level throughout the experiment. In this way, only a small amount of water was exposed to the air in the recording system.

Calibration.—In most of the previous investigations with the hand plethysmograph[5, 9, 13] the recording system was calibrated by injecting 1 to 5 c.c. of air into the tubing leading to the Brodie's bellows and then applying the scale thus obtained to determine the rate of increase of the hand volume (as represented on the drum) when the collecting pressure was applied. This method is open to criticism if absolute blood flow figures are desired, since a 1 c.c. increase in hand volume does not produce as great a rise of the lever as does an injection of 1 c.c. of air into the tubing leading to the Brodie's bellows, for the following reason: when the hand volume is increased, an equal volume of water is displaced, only part of which in turn displaces its equivalent volume of air in the recording system. The rest tends to distend or somewhat stretch the membrane through which the hand passes, even when it is supported by the felt pad and iris diaphragm. As a result, the entire volume change is not represented in the graph (for explanation see below). Furthermore, since the tension of the rubber membrane will most likely be different in each experiment (resulting in variations in the sensitivity of the apparatus), while the calibration with the above method will always remain constant, another source of error may be introduced if comparisons of absolute blood flow determinations are made under these conditions. However, for any experiment which is complete in one trial, relative figures will have some significance.

In the present investigation calibrations were made under conditions similar to those of the blood flow measurements. In other words, each plethysmograph was calibrated with the extremity in place by permitting water from the burette to enter the machine in 2 c.c. amounts and recording the rise of the lever with each increment. In the case of the hand, since oscillations resulting from the heart beat as well as spontaneous variations in vasomotor tonus tended at times to introduce a large error, a pressure of 200 mm. Hg was generally introduced into a cuff on the arm during the period of calibration in order to obstruct all flow of blood into the extremity. In the case of the foot or forearm, such precautions were generally not necessary because spontaneous changes in the baseline were not marked. The calibrations thus obtained were used as a basis for forming a scale in which each subdivision was equal to 0.25 c.c.; the sensitivity of the recording system was such that the lever of the bellows rose about 15 mm. on the drum with each volume change of 1 c.c. in the plethysmograph. By means of this scale the rate of peripheral blood flow was calculated by measuring the height of average rise from the baseline of each curve at the end of the first second following the application of the collecting pressure. The initial portion of the tracing was the most rapid in its ascent and consequently

more nearly represents unopposed arterial inflow. All tracings which curved upward for a short period of time (one second, or so) and then flattened out to form a plateau were discarded because they most likely indicated the presence of an abnormally large quantity of blood in the venules and veins. This would tend to oppose the flow of blood into the extremity and hence contribute toward low blood flow determinations. The figures obtained from records considered satisfactory were then converted into flow per minute and flow per minute per 100 c.c. of limb volume. The volume of the hand or forearm was readily obtained by subtracting the amount of water necessary to fill the plethysmograph with the extremity in place from the figures representing the capacity of the apparatus. The foot-leg volume was obtained by inserting that part of the extremity previously in the plethysmograph into a large container completely filled with water and measuring the displacement volume. Generally, the hand volume varied from 350 to 550 c.c., the forearm from 400 to 600 c.c., and the foot-leg volume from 1200 to 1800 c.c.

Diameter of Glass Tube of Recording System.—The fact that a large glass tube was used in each plethysmograph to join the rubber tubing connected with the Brodie's bellows to the apparatus has been purposely stressed, for it was found that when a small tube (about 0.5 cm. in diameter) was substituted for the one in the hand or forearm plethysmograph (2.2 cm. in diameter) the sensitivity of the recording system was markedly diminished. For example, the entrance of 2 c.c. of water from the calibrating burette into the hand or forearm plethysmograph generally caused the lever (of a constant length) connected to the Brodie's bellows to rise about 30 mm. with the larger tube in place, but this response was diminished to 9 mm. with the smaller tube. In fact, if a narrow tube was utilized with the foot plethysmograph, the sensitivity of the entire system was so slight as to make it almost impracticable for use. The cause for this difference in response is partly the same as that which accounts for the marked variations between water and air calibrations. For, as has been stressed, the plethysmograph is not a chamber of fixed capacity, since it has one wall (in the case of the forearm, two walls) composed of rubber membrane which remains distensible. Consequently, during a blood flow determination, when a rise in the height of the column of water in the glass tube takes place there is an increase in the hydrostatic pressure of the system, which in turn further stretches the membrane. As is obvious, the entrance of equal quantities of water into a large and a small tube, respectively, will result in a much greater increase in hydrostatic pressure in the latter, and hence produce a greater distention of the membrane, with a less marked effect upon the recording system.

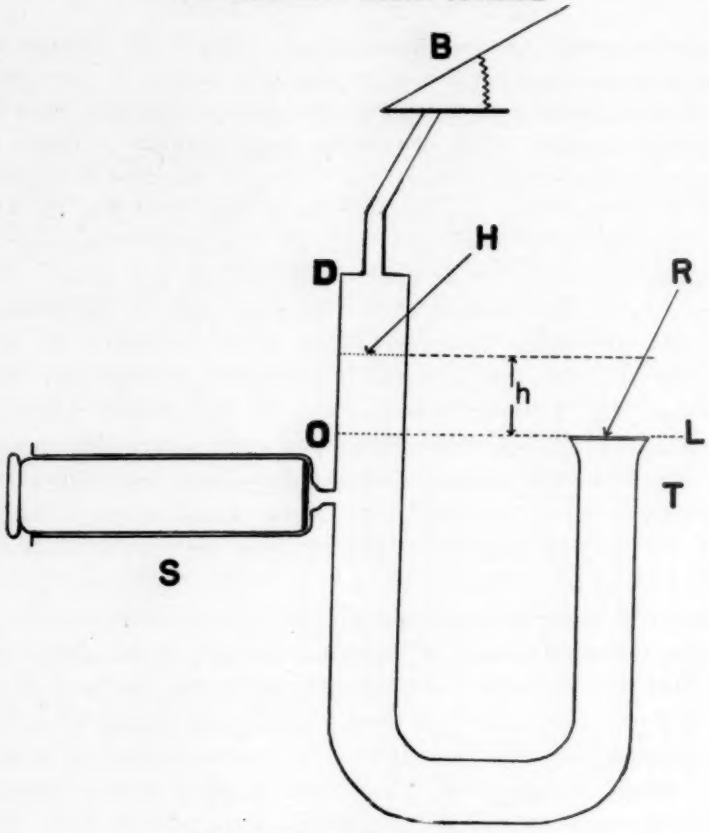

Fig. 4.—See text for explanation.

The explanation for the above findings can be presented more simply by means of a substitute system (Fig. 4) which has all the essential physical properties of the plethysmograph and its recording mechanism. The plethysmograph itself is represented by the U tube, *T*, one limb of which is covered at its upper end by a rubber membrane, *R*, the equivalent of the elastic pocket formed by the rubber diaphragm of the plethysmograph. The syringe, *S*, is utilized to deliver a definite volume of water to the apparatus, imitating the swelling of the extremity during a blood flow determination. *OD* is the equivalent of the tube leading to the Brodie's bellows from the plethysmograph. The water level, *H*, in this tube acts like a piston to displace a volume of air which in turn raises the Brodie's bellows, *B*, with its attached lever. Now, if a rigid membrane is substituted for the rubber one, *R*, then the addition of a definite volume of water to the U tube (previously filled with water to the level, *L*) will cause the water to rise a certain height, *h*, in *OD*. If the rubber membrane is now replaced and the same step performed, the rise in *OD* will be greater than $\frac{h}{2}$ but less than *h* for the following reason:

The rubber membrane will be exposed to a force which tends to distend it, thus increasing the volume capacity of the space bordered by the membrane. The magnitude of this force is determined by the difference in height of the points *H* and *R*, equal to *h*; the larger *h* is for a given injected volume, the greater is the force, and hence the elastic loss. The greater the diameter of *OD*, the smaller is *h* for the same injected volume. Therefore, it follows that the loss will become less and less, as the cross section of *OD* increases.*

*We are indebted to Dr. A. Kolin of Mt. Sinai Hospital for the above explanation.

By applying the various plethysmographs to the limbs as described above, blood flow determinations which are representative of different combinations of peripheral blood beds can be obtained. For instance, in the case of the hand, the predominant flow is through the skin and subcutaneous tissues, which, according to Grant and Pearson,[12] make up about 50 per cent of the volume of the fingers. On the other hand, figures obtained for the upper portion of the forearm will indicate largely the flow through muscle, since about 85 per cent of the volume is made up of this tissue.[12] Finally, in the case of the lower extremity, with all of the foot and part of the leg in the plethysmograph, a composite type of response will be elicited.

By obtaining blood flow measurements in a foot and hand, or a foot and forearm, a means is at hand for determining simultaneously the effect of various physiologic procedures upon the different types of blood beds. Further, by varying conditions to which one extremity is exposed, distant effects on blood flow can be observed as manifested by changes in the other.

SUMMARY

The various pitfalls associated with plethysmographic determinations of blood flow in the extremities are presented. The criteria used to recognize and eliminate artifacts in the records are discussed.

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PLETHYSMOGRAPHIC STUDIES OF PERIPHERAL BLOOD FLOW IN MAN

II. Physiologic Factors Affecting Resting Blood Flow in the Extremities*

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IN A preceding paper[1] attention was called to the mechanical and physical difficulties in the use of the plethysmograph which might lead to erroneous determinations of blood flow measurements in the extremities. In addition to these, there are numerous physiologic factors which may also produce marked variations. In the present report these are described and means of control or elimination suggested, in order that significant and reproducible data may be obtained. As reported in the previous paper,[1] the foot plethysmograph was used in conjunction with either a forearm or hand apparatus.

1. *Spontaneous Variation in Vasomotor Tonus.*—One of the most important factors contributing to variations in blood flow is the spontaneous changes in vasomotor tonus occurring during the period of observation. This is especially so in the case of the hand, which, because of its relatively large area of highly specialized skin with many arteriovenous shunts, is particularly responsive to impulses from the vasomotor center. In order to minimize this extraneous influence, blood flow measurements were made with the blood vessels in the hand relatively dilated. This state was determined when the baseline of the recording system spontaneously reached its highest level, indicating a maximal blood volume in the extremity as a result of more rapid blood flow through it per unit of time. Once this level was observed, it was used throughout the experiment. Possible errors arising from spontaneous variations were further obviated by recording at least thirteen to fifteen consecutive resting blood flow measurements and computing the average of the figures. In the case of the foot and forearm these difficulties are not encountered to the same extent.

2. *Effect of Painful Stimuli.*—Fluctuations such as are observed during the period when the skin is being prepared for insertion of a needle into a vein, or during the actual procedure of injection, cannot be entirely eliminated, but they may be obviated somewhat by using subjects who are stolid and have previously been exposed to many similar tests.

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Since painful stimuli generally produce vasoconstriction,[2] a decrease in blood flow during these periods is given little consideration in the interpretation of the data.

3. *Effect of Varying Temperature of Water in Plethysmographs (Bath Temperature).—A.* Flow at 32° C. Since it was found that exposing the extremity in the plethysmograph to the low bath temperature (20 to 25° C.) used in some studies produced a marked slowing of blood flow, it was decided to adopt more nearly physiologic conditions by maintaining the temperature of the water at the same level as that of the skin, namely, at 32° C. Examination of Table I reveals that the average flow per minute per 100 c.c. of limb under these conditions is greatest in the hand, less in the foot (including the lower portion of the leg) and least in the forearm (Fig. 1). In some instances, following the above

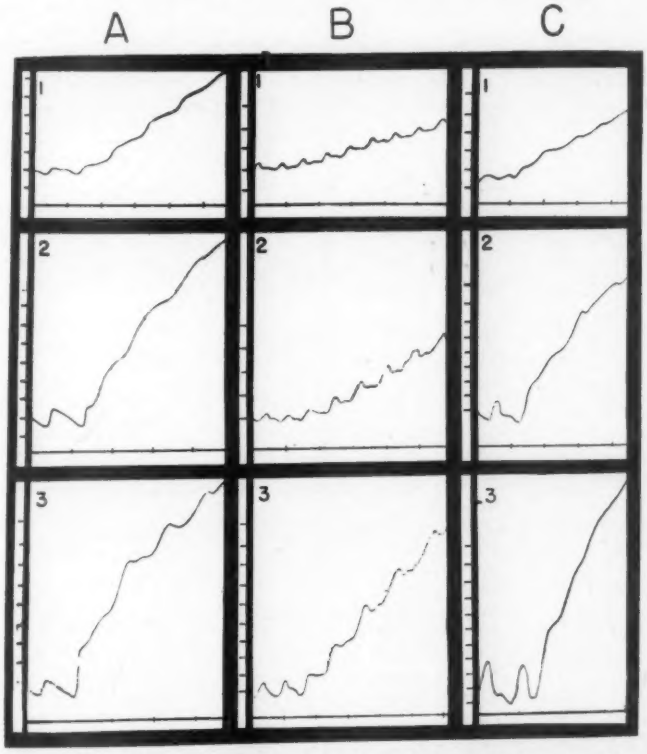

Fig. 1.—Effect of varying bath temperature in plethysmographs upon blood flow in hand, forearm, and foot (with portion of leg). Subject L. S.

	(1) FLOW AT 32°C. (C.C.)	(2) FLOW AT 32°C. WITH VESSELS REFLEXLY DILATED (C.C.)	(3) FLOW AT 45°C. (C.C.)
A, right hand (vol. 430 c.c.)	10.6	27.3	33.0
B, right forearm (vol. 600 c.c.)	2.5	4.7	11.1
C, left foot (vol. 1450 c.c.)	4.9	10.1	15.2

All figures represent the number of cubic centimeters of blood flow per minute per 100 c.c. of limb volume. Time in seconds. Calibrations, 1 division equals 0.5 c.c.

step reflex vasodilatation of one or both extremities in the plethysmographs was then produced by applying heat to other portions of the body for at least three-quarters of an hour.[3, 4] Generally, an increase in blood flow was obtained which was especially marked in the hand and less so in the forearm and foot (Fig. 1), which observations are in accord with those of Grant and Pearson.[5] In the case of four subjects on whom paravertebral block had been performed previously, this phenomenon was not elicited in the anesthetized foot. These findings in the lower extremity are further confirmatory evidence for the statement that reflex vasodilatation depends upon the integrity of vasomotor nerves, a view which is based upon observations in the normal and sympathectomized hand.[3, 6, 7]

TABLE I

RESTING BLOOD FLOW MEASUREMENTS AT BATH TEMPERATURES OF 32° AND 45° C. AND ROOM TEMPERATURE BETWEEN 25° AND 27° C.

SUBJECT	AGE	HAND			FOREARM			FOOT-LEG		
		NO. OF TRIALS	FLOW AT 32°	FLOW AT 45°	NO. OF TRIALS	FLOW AT 32°	FLOW AT 45°	NO. OF TRIALS	FLOW AT 32°	FLOW AT 45°
K. M.	24				3	2.4	7.2	1	5.4	13.9
L. S.	50	4	14.8	33.2	3	2.3	12.8	12	4.2	15.0
V. B.	29				2	1.7	6.8	1	4.0	
R. T.	23				2	2.3	11.8			
N. G.	22				3	1.8	7.1	1	5.0	
D. G.	21				2	3.1	7.8	1	3.0	
J. M.	28	2	10.3	39.0				1	1.3	9.9
F. A.	30							1	2.4	17.2
S. S.	42	6	21.9	39.2						
L. N.		2	19.1	38.3				1	6.6	10.5
R. W.	19							1	3.6	
A. S.	23							1		15.6
P. S.								1	4.7	
L. K.		2	19.1	35.5				2	3.3	14.9
A. B.	44	8	10.5	41.0				9	3.9	
J. G.	22	2	11.0					1	5.8	
M. S.	26	4	11.2							
J. T.	41	2	10.0							
E. R.	36	2	15.0	37.5						
H. F.		7	16.9	39.6						
P. M.	50	7	19.7	34.7						
S. N.	38	3	18.1	34.1						
R. G.	27	2	10.1	40.5						
F. A.		2	13.0	39.8						
F. S.		1	12.2	41.9						
H. L.	38	8	11.5	33.1						
S. R.	33	4	9.1	37.1						

All figures represent blood flow per minute per 100 c.c. limb volume.

B. Flow at 45° C. When the flow at 45° C. is compared for the three sites (Table I), that in the hand is uniformly greater than that in either the foot or forearm; this difference is probably due to the greater quantity of blood flowing through the specialized skin vessels of the fingers. As noted in Table I, the range of normal blood flow measurements in the hand varies to a much greater extent when the bath temperature is 32° than when it is 45° C. This may be ascribed to the

probability that fluctuations in vasomotor tonus are more apparent at the lower temperature. Further evidence for this view is the fact that spontaneous variations in the baseline generally observed at 32° are practically absent at 45°.

4. *Effect of Varying Environmental Conditions.*—Other factors which must be controlled in order to obtain comparable blood flow readings are the relative humidity (which should be around 50 per cent) and the temperature of the room. The most satisfactory range for the latter for obtaining stable results is between 25 and 27° C., for under these conditions there is neither marked peripheral vasconstriction nor dilatation. If the temperature drops a degree or more below the lower limits, the resting flow at a bath temperature of 32° is significantly diminished, or if it rises much above 27° the flow tends to approach in magnitude that obtained with reflex vasodilatation. In certain respects these last two states (i.e., flow at high room temperatures and that with reflex vasodilatation) are similar, one merely representing a somewhat more marked stage of the other.

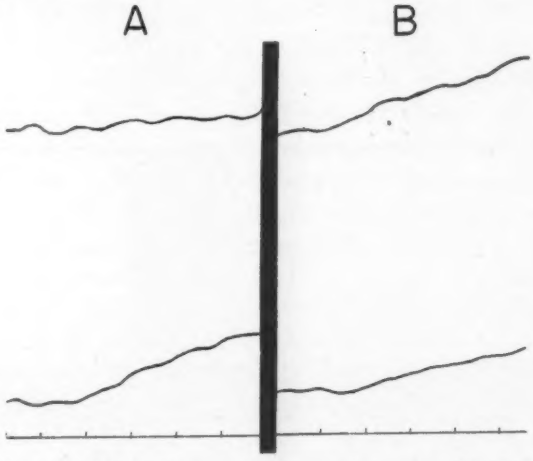

Fig. 2.—Effect of varying environmental temperature upon blood flow in a subject (H.L.) abnormally sensitive to cold. *A*, Room temperature of 21 to 24°. Upper graph, flow in right hand (vol. 480 c.c.) 4.6 c.c. Lower graph, flow in left foot and adjoining portion of leg (vol. 1300 c.c.) 3.1 c.c. *B*, Room temperature of 25 to 27°. Upper graph, flow in right hand (vol. 450 c.c.) 12 c.c. Lower graph, flow in left foot and portion of leg (vol. 1350 c.c.) 2.6 c.c. Time in seconds. Bath temperature 32°.

An exaggerated example of the effect of lowering room temperature on blood flow is demonstrated by the responses of a subject (H. L.) who reacted markedly to cold (Fig. 2-B). In the case of the right hand, the average resting blood flow was 4.6 c.c. per minute per 100 c.c. of limb when the temperature of the room varied between 21° and 24°, and 12 c.c. at a range between 25° and 27° C. (average of six experiments for each range of temperature). Likewise, in the left hand, it was 3.9 c.c. (average of four experiments) at the lower room temperature, and 11.1 c.c. (average of five experiments) at the higher level. The differ-

ences in the feet were not as marked, which may have been due partly to the presence of a paravertebral block on both sides. In the right foot the flow was 2.5 c.c. (average of four experiments) at the lower, and 3.4 c.c. (average of five experiments) at the higher ranges, while in the left it was 1 c.c. (average of two experiments) and 3.6 c.c. (average of six experiments) at the lower and higher temperatures, respectively. In every instance the portion of the extremity in the plethysmograph was exposed to water at a constant temperature of 32° C., but evidently the flow through it was affected by raising or lowering the temperature of the air surrounding the rest of the body. When the bath temperature was raised to 45°, however, there was no significant difference between the figures obtained at the high and low room temperatures. This was so in the case of all the sites studied. In other words, vasomotor changes resulting from variations in environmental conditions are ineffective in the presence of the strong vasodilatation produced by the direct application of heat. At this point, therefore, it must be emphasized that many variables can modify blood flow measurements of the hand, at least at a bath temperature of 32° (the one frequently employed in plethysmographic studies); on the other hand, at 45° the determinations are less affected by extraneous factors and hence indicate more accurately the actual state of the peripheral circulation.

5. *Local Reflex Effect Elicited by Application of Occlusion Pressure to Lower Extremity.*—It was noticed during the preliminary work of obtaining measurements in the lower extremity at 32° that after the release of the occlusion pressure the lever quickly fell to the level of the previous baseline, and then dropped much below, to return slowly. This finding, indicating a decrease in limb volume, was generally present in foot records of many normal subjects (Fig. 3) and was occasionally observed in the hand as well. In order to investigate the matter, gradually decreasing pressures were applied to the leg until a level finally was reached which produced no increase in the foot-leg volume, i.e., was not sufficient to cause any obvious venous occlusion. However, even under these circumstances releasing the pressure resulted in the drop below the baseline (equivalent to a decrease of 0.5 to 2 c.c. of limb volume) and a return in from fifteen seconds to two minutes (Fig. 4). Occasionally a rise above the baseline followed the drop. The degree of response could not be correlated with either the height of the pressure or the previous duration of application of this pressure.

This phenomenon was then studied in a series of four patients in whom paravertebral block of the lower extremities had been produced previously. In each instance, upon application of the occlusion pressure to the anesthetized leg the same reflex was elicited (Fig. 3, *2*). On the other hand, when the temperature of the water in the foot plethysmograph was raised to 45°, in these patients as well as in normal subjects, the momentary drop in foot volume was no longer observed (Fig. 3, *3*).

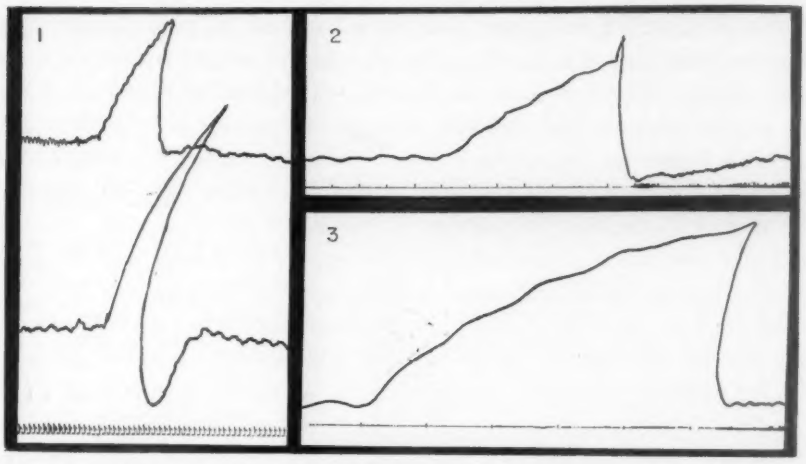

Fig. 3.—Effect produced by the application of occlusion pressure. *1*, Upper graph, flow in hand following application of occlusion pressure of 70 mm. Hg to wrist for nine seconds. No drop in baseline below previous level on release of pressure. Lower graph, flow in foot following application of occlusion pressure of 110 mm. Hg. Definite drop in baseline below previous level on release of pressure and then a gradual return. *2*, Application of occlusion pressure of 110 mm. Hg to right leg (paravertebral block produced two months previously). Definite drop in baseline below previous level on release of pressure and then a gradual return. All readings obtained at bath temperature of 32°. *3*, Application of occlusion pressure of 110 mm. Hg to leg with the bath temperature at 45°. No drop in baseline below previous level on release of pressure. Time in seconds.

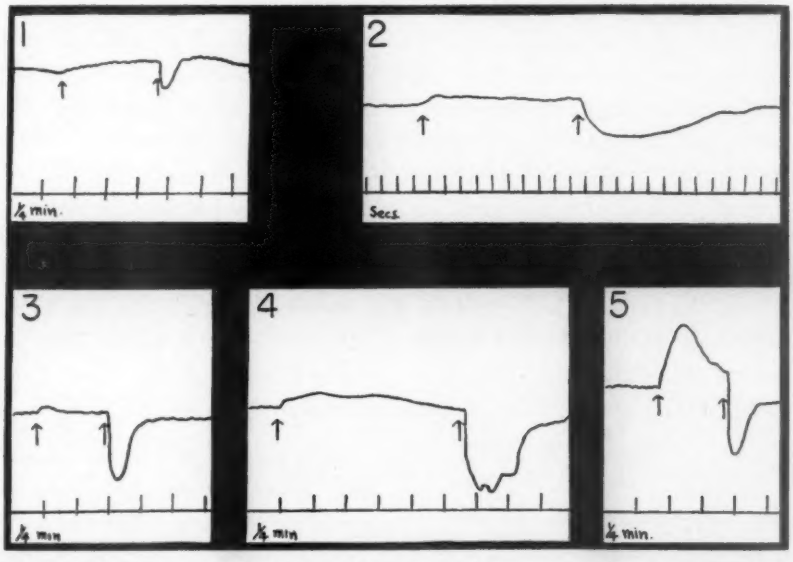

Fig. 4.—Effect produced by the application of different amounts of pressure to the leg (in which paravertebral block had been produced previously). Bath temperature, 32°. Duration of pressure indicated by arrows. *1*, Application of 30 mm. Hg; *2*, application of 35 mm. Hg; *3*, application of 40 mm. Hg; *4*, application of 45 mm. Hg; *5*, application of 50 mm. Hg.

In every instance a drop in baseline (denoting a decrease in volume of the extremity) is noted upon release of the pressure. In record *1* a rise above the baseline follows the drop.

This response, therefore, is probably due to vasoconstriction of the blood vessels in the foot as a result of the elicitation of some local reflex.* Whether the effect is upon the arteriolar or the venous bed has not been determined. That it is not due to passive drainage of blood away from the leg is supported by the fact that the extremity is in a dependent position, which would oppose such a tendency. Since the reaction can be produced by the application of a pressure so low that no change in the volume of the foot is observed, it does not seem reasonable to assume that the provoking mechanism is stretching of the vessel wall by an increased intravascular pressure. Comparison of this response with that resulting from a pinch of the skin, as described by Capps,[9] reveals certain differences between the two. For, whereas in the latter procedure vasoconstriction is obtained immediately upon the application of the painful stimulus to the arm, in the former the response is observed upon removal of the pressure, and then generally only in the case of the foot. It is of interest that the volume change produced by the pressure is abolished by local heat. Evidently the exaggerated vasodilatation resulting from the latter procedures is sufficient to overcome any vasoconstriction produced reflexly. These findings are further proof for the belief that blood flow determinations obtained at a bath temperature of 45° C. are more stable and more significant than those obtained at other temperatures.

6. *Effect of Increase in Local Venous Pressure.*—In a patient, A. G., suffering from carcinoma of the lung and metastasis to the lymph nodes of the right axilla, an opportunity was offered to observe the local effect of increased venous pressure upon blood flow in an extremity. The enlarged lymph nodes were evidently producing pressure upon the veins and causing a discernible swelling of the skin and subcutaneous tissue of the right arm. The venous pressure was 190 mm. of water in this extremity as compared with 120 mm. in the left, while the arterial pressure was the same in both. Blood flow measurements in the hands were obtained on three different occasions, the order with which they were recorded being changed each time. In every instance, the blood flow in the right hand was definitely and significantly greater than that in the left; the average for the former was 12.9 c.c. per min. per 100 c.c. of limb as compared with 7.3 c.c. for the latter (Fig. 5).

The fact that blood flow may be increased in an extremity in which the venous pressure is high may possibly be explained on the following basis: A rise of pressure within the veins and venules causes them to become distended because of the looseness of the tissues supporting

*This finding may be of more than academic interest in respect to the widely used method of intermittent venous occlusion[8] in the treatment of peripheral vascular disease of the lower extremities. That a reflex which produces vasoconstriction is elicited by a procedure grossly similar to that utilized in the method suggests that the physiologic rationale for this treatment should be subjected to further investigation.

them. As a result, there is stasis of blood in these vessels (since for equal quantities of blood flowing into the veins the velocity will be inversely proportional to cross-sectional area) with consequent anoxemia of the tissues. Possibly then, in response to stasis and tissue anoxemia, a state comparable to reactive hyperemia[10] is brought about, which in turn affects the caliber of the terminal arterioles and thus causes a compensatory increase in local arterial blood flow.

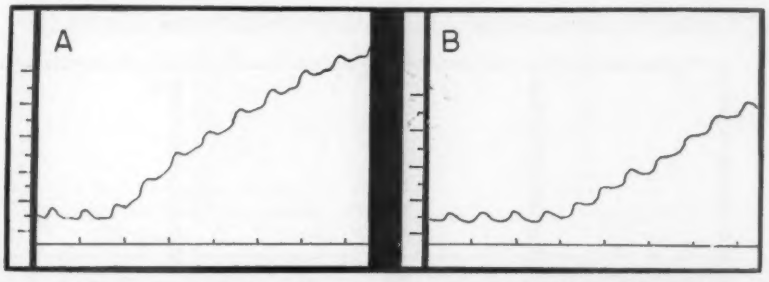

Fig. 5.—Effect of increased venous pressure upon blood flow. Subject (A.G.) with carcinoma and metastasis to lymph nodes in the right axilla producing increased venous pressure in right upper extremity. *A*, Blood flow in right hand (vol. 550 c.c.) 14.4 c.c. Venous pressure, 190 mm. water. *B*, Blood flow in left hand (vol. 550 c.c.) 7.1 c.c. Venous pressure, 120 mm. water.

7. *Variations in Blood Pressure.*—We were fortunate to have at our disposal a woman patient, aged 26, who was found to have a brachial blood pressure ranging between 160 and 230 mm. Hg systolic and 120 and 130 mm. Hg diastolic in the right arm, and between 120 and 130 mm. Hg systolic in the left arm; the diastolic level was difficult to obtain in the left arm. The cause for this phenomenon could not be ascertained with certainty, although the possibility of a generalized hypertension with some obstruction to the flow in the left arm was entertained, since the pressure in the legs was also elevated. There was no apparent difference in the color of the skin or the size and muscular development of the two arms, although the pulse was much more difficult to palpate in the left and there was a discernible delay in its arrival. Nevertheless, the blood flow in the two hands was identical [i.e., within the range of experimental error (Fig. 6)], a finding which was anticipated in view of the similarity in the size and appearance of the two extremities. Measurements were then obtained after the application of a pressure of 200 mm. Hg to each arm separately for ten minutes in order to produce reactive hyperemia (Fig. 6). In the left hand the greatest flow after release of pressure was 19.4 c.c. per minute per 100 c.c. of hand (average resting flow 4.8), whereas in the right it was 30 c.c. (average resting flow 5.4); i.e., the flow in the right was 50 per cent greater than in the left under these conditions. The results obtained during reactive hyperemia suggest either a constantly existing state of exaggerated vasoconstriction of the blood vessels in the right hand,

or more probably a compensatory vasodilatation in those of the left hand. As a result, blood flow through each extremity per unit of time was the same despite marked differences in blood pressure. This case demonstrates to a certain degree the influence of one type of abnormality of the blood vessels upon blood flow in the extremities.

8. *Ingestion of Food.*—In view of the well-known effect of the ingestion of food upon cardiac output, an attempt was made to keep this factor as constant as possible by beginning all experiments about the same time after the last meal (two and one-half hours).

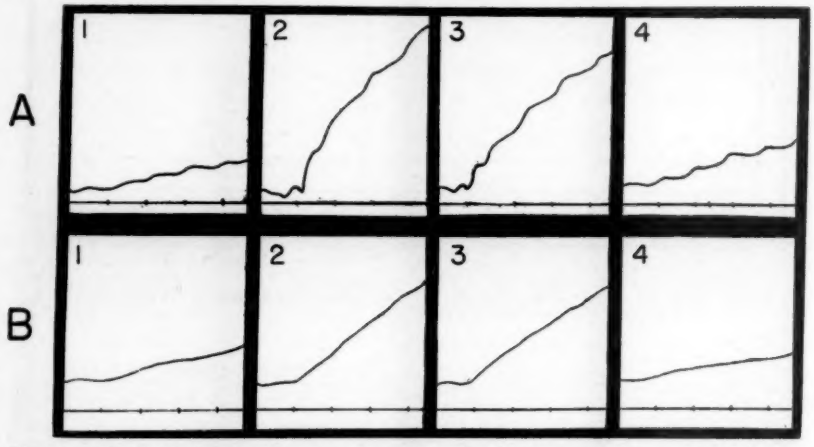

Fig. 6.—Effect of different levels of systolic blood pressure upon resting blood flow and flow after reactive hyperemia (subject R. B.). Blood pressure in right arm $\frac{210}{140}$, and in the left $\frac{130}{?}$. Bath temperature, 32°. *A*, Blood flow in the right hand (vol. 400 c.c.). *1*, Resting blood flow, 5.4 c.c. Records *2*, *3*, and *4* obtained at 30 seconds (flow, 30 c.c.), 70 seconds (flow, 22.5 c.c.), and 190 seconds (flow, 7.5 c.c.), after removal of a pressure of 200 mm. Hg applied to the right arm for ten minutes in order to produce reactive hyperemia. *B*, Blood flow in the left hand (vol. 350 c.c.). *1*, Resting flow, 4.8 c.c. Records *2*, *3*, and *4* obtained at 30 seconds (flow 19.4 c.c.), 70 seconds (flow 14.5 c.c.) and 190 seconds (flow 4.8 c.c.), after production of reactive hyperemia as in *A*. Time in seconds.

9. *Sleep.*—Another factor which it was found necessary to control was the state of consciousness of the subject. Dozing or actual sleep in some instances produced a decrease in blood flow, especially in the upper extremities (Fig. 7); this drop was even more accentuated by sudden awakening. Further evidence for the presence of a diminished flow was a concomitant drop in the level of the baseline (indicating a smaller limb volume) and a flattening out of the oscillations normally present in the records (Fig. 7).

10. *Shock.*—As has been reported,[2, 11] in the presence of shock the blood flow to the periphery is markedly reduced. In circulatory collapse induced by sodium nitrite[11] the responsible mechanism is a pooling of blood in the venules and veins (resulting in reduced venous return and hence diminished cardiac output) coincident with reflex arteriolar constriction. These factors also play a role in surgical shock. During the course of a study on the influence of vasodilator drugs, we

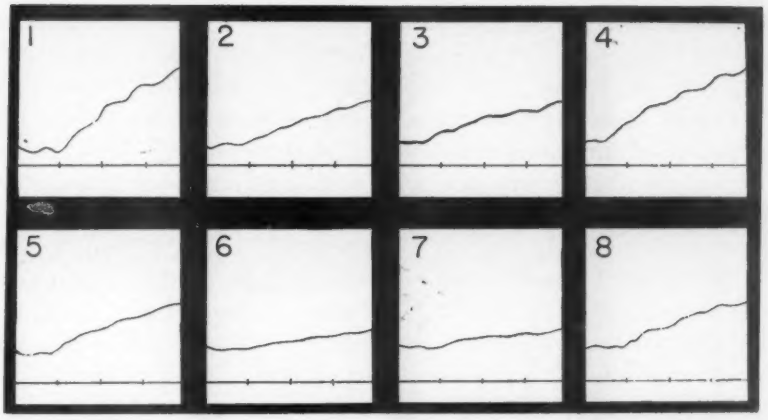

Fig. 7.—Effect of sleep upon blood flow in the left hand (subject A. K.). Bath temperature, 32°. *1*, Resting blood flow (vol. 465 c.c.) 12.4 c.c. Records *2* to *7*, inclusive, taken during period in which subject was asleep. *2*, Blood flow, 6.5 c.c; *3*, blood flow, 5.8 c.c.; *4*, blood flow, 9.8 c.c.; *5*, blood flow, 6.5 c.c.; *6*, blood flow, 2.6 c.c.; *7*, blood flow, 3.2 c.c.; *8*, taken after patient was awakened, blood flow, 7.9 c.c. Time in seconds.

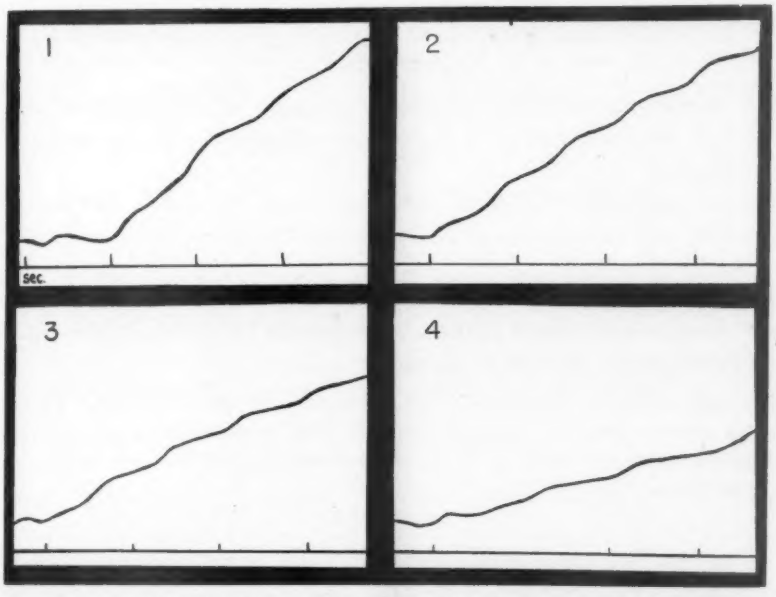

Fig. 8.—Effect of diminished cardiac output (as a result of shock) upon peripheral blood flow (subject H. L.). Blood flow in right foot (vol. 1450 c.c.). Bath temperature, 45°. *1*, Control blood flow, 11.3 c.c. Records *2*, *3*, and *4* taken at varying intervals after onset of symptoms of shock. *2*, Five minutes after, 7.4 c.c.; *3*, seven minutes after, 7.7 c.c.; *4*, twenty-four minutes after, 3.3 c.c. Time in seconds.

had the occasion to observe a subject who went into shock as a result of a slightly different mechanism. In this individual, H. L., two extremities in plethysmographs were exposed to a bath temperature of 45° C. for about one hour, and then 1 c.c. of "spasmalgin" (combination of atropine, pantopon, and papaverin) was injected intravenously. Immediately upon the completion of this procedure, the patient began to complain of weakness and palpitation, became pale, and the blood pressure fell. During this period blood flow in the lower extremity was definitely reduced (Fig. 8). The decreased peripheral flow in this instance was evidently due to a diminished venous return, resulting from the marked vasodilatation produced both by the heat and the drug. It is improbable that any effective vasoconstriction could occur in the extremities in the plethysmographs because of the counteracting local vasodilatation. Indirect evidence for this view is the fact that the oscillations in the blood flow records, which are coincident with the heart beat, were only slightly changed in amplitude during the period of diminished flow; for these oscillations are primarily influenced by alterations in caliber of blood vessels and to a much lesser degree by cardiac output. This experience, therefore, emphasizes the effect of changes in cardiac output upon peripheral circulation. As is obvious, this factor is as important as the state of the blood vessels in determining the resultant rate of blood flow.

SUMMARY

The various physiologic factors which may modify normal resting blood flow determinations are discussed, and methods for obviating them are presented.

The normal ranges of blood flow values for the hand, forearm, and foot under different states of vasomotor control are presented and their significance discussed.

A local reflex is described which produces vasoconstriction of the blood vessels of the lower extremity on release of the occlusion pressure used in obtaining blood flow figures.

The authors wish to express their appreciation to Dr. Mae Friedlander for help in carrying out the preliminary experiments, and to Dr. S. Silbert, who was instrumental in supplying them with many of the patients studied and contributed numerous helpful suggestions.

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THE USE OF MAGNESIUM SULFATE IN THE MEASUREMENT OF CIRCULATION TIME*†

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THE subject of blood flow has fascinated the medical profession since Harvey's time. It is only within the last decade, however, that methods easily applied clinically have superseded the older, more cumbersome and inaccurate methods for determining the blood velocity, or its inverse equivalent, the circulation time. By the latter term is meant the interval of time necessary for a particle of blood to transverse a given distance.

The methods most commonly used hitherto depend upon the rapid injection of a foreign substance in an antecubital vein and its detection at the point of reaction. The type, as well as the site, of reaction varies considerably with the substance used, viz., the substance's color,[1] vasodilator effect,[3, 50] radio activity,[4, 5, 6, 52] effect on respiration,[4, 7, 8, 9, 10] neuromuscular stimulation,[11-14] smell,[15-19, 49] or taste.[20, 15, 21-24, 17, 25-32] It is this very difference in results and site of end point that has led to considerable confusion in the literature.

During the course of clinical research with magnesium in cardiovascular-renal disease we were struck with the sharp reaction patients developed during the intravenous injection of a 10 per cent solution of magnesium sulfate. Its possible use as an agent for the determination of the circulation time having suggested itself, we pushed its application in a variety of clinical conditions and finally perfected a standard technique. After the work was well under way, a further perusal of the recently indexed literature disclosed that the use of magnesium as a circulation-time agent had been suggested abroad by Zwillinger[33] and applied, with somewhat different technique from ours, by Neurath[34] in a group of cardiac cases.

PROCEDURE

Five hundred seventy-nine magnesium sulfate circulation-time determinations were performed in 274 patients, 126 of whom were of the cardiac class. Space does not permit the publication of all the data in this study, but illustrative cases are detailed. Most of the subjects were ward patients; a small group of ambulatory hypertensive patients was studied in the outpatient department. Three hundred twenty-nine tests were performed in the cardiac group and 250 in a heterogeneous noncardiac group. To check the efficacy of magnesium, 85 determinations of the cal-

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cium gluconate circulation time were performed in the cardiac group and 38 in the noncardiac group. Fifty-seven ether circulation-time tests were done in the cardiac cases, and 80 in the noncardiac.

TECHNIQUE

The patient reclines as nearly as possible flat in bed, with the arm at the level of the right auricle. The patient must relax and not hold his breath as this retards the venous return to the heart. He is told that he will experience a transient hot sensation in the pharynx and tongue that spreads rapidly downward, and he is instructed to announce the onset of the sensation in the pharynx at once by crying "now." The tourniquet is applied, the needle inserted, and the injection (slightly warm) given after the lapse of a few seconds. Six cubic centimeters* of a 10 per cent solution of magnesium sulfate are injected as *rapidly as possible* with a needle (preferably 18 gauge) and a 10 c.c. syringe. The time is recorded with a stop watch from the beginning of the injection, rather than at the conclusion or midway during the injection, because even a minimal amount of the drug may evoke a strong reaction in many patients. To insure accuracy when the test is performed by one person unassisted it has been our practice to start the stop watch and to begin the injection at the moment the hand of the stop watch is crossing the five-second mark. The five seconds are subtracted from the circulation time that is finally recorded. In this way the one who performs the test has at his disposal both hands, thus facilitating a rapid, accurate injection. The time required for the completion of the injection is usually less than two seconds. In sensitive patients even as little as 2 c.c. often gives as rapid a circulation time as 6 c.c. On the other hand, repeated trial has shown that 6 c.c. is the optimum amount for consistent results in markedly decompensated patients, the larger quantity being necessary to build up the blood concentration for a sharp end point.

The feeling of heat in the pharynx is extremely sudden in onset and often so intense that in numerous cases the patient's sudden start is indication enough that the end point has been reached. The "heat" follows progressively the course of the peripheral arterial beds, being felt next in the face, one or both hands or perineum, and finally in the feet. This very progressiveness of sensation suggests the possible use of magnesium in measuring the circulation times to the extremities. The sensation is transient, passing off within ten to twenty seconds. The test may be repeated within a few minutes with practically duplicate results. Although we have never observed any magnesium idiosyncrasy to date, we are always provided with an ampoule of a 10 per cent solution of calcium gluconate (the physiologic antagonist of magnesium) for immediate intravenous use should such a reaction occur.

The calcium circulation time is performed in similar fashion, 2.5 c.c. of a 20 per cent solution of calcium gluconate being used as recommended.[13, 21, 35] To obviate any possibility of the calcium affecting a succeeding magnesium test, and vice versa, we alternated the two agents at random, one test being carried out within a short time after the completion of the preceding one. We observed no effect of one agent upon the other. The sensation produced by calcium is quite similar to that produced by magnesium, though rarely as marked in intensity or suddenness of onset.

The ether circulation time is determined by the intravenous injection of 5 minims of ether mixed with 5 minims of normal saline.[15-18] A tuberculin syringe and a large needle are employed. The time is recorded from the moment of injection until the patient signals that he smells ether on his breath. Usually this is accompanied by a cough or grimace. At the same moment the observer can smell the ether. The ether test thus has the advantage of being both objective and subjective.

*In the early stage of the work ampoules of a 10 per cent solution of magnesium sulfate were purchased on the market. In the latter stages we prepared a 10 per cent C. P. magnesium sulfate solution in distilled water, stored it in ampoule vials, and autoclaved it. This method provided, at practically negligible cost, a solution that gave perfectly satisfactory results.

TABLE I

DETAILED ANALYSIS OF MAGNESIUM AND CALCIUM CIRCULATION TIMES IN NONCARDIAC GROUP

DIAGNOSIS	NO. OF CASES	NO. OF TESTS MAG.	NO. OF TESTS CALC.	MAGNESIUM CIRCULATION TIME			CALCIUM CIRCULATION TIME		
				LOW (SEC.)	HIGH (SEC.)	AVERAGE (SEC.)	LOW (SEC.)	HIGH (SEC.)	AVERAGE (SEC.)
Normal:									
Cholelithiasis (uncomplicated)	6	11	2	8.6	17.8	13.4			
Diabetes mellitus (uncomplicated)	4	7	0	11.2	16.0	13.4			
Nephroptosis	4	7	2	11.0	12.4	11.8			
Hepatomegaly (noncardiac)	5	6	2 (1 fail.)	10.8	17.0	13.7	13.0	14.8	13.9
Miscellaneous	72	132	16 (2 fail., 1 partial fail.)	7.0	19.8	12.8	10.0	17.2	14.8
Total	91	163	22 (3 fail., 1 partial fail.)	7.0	17.8 (1 case = 19.8)	12.9	10.0	17.2	14.2
Allergic:									
Bronchial asthma	7	10	3 (1 fail.)	8.2	14.0	11.6	11.6	17.0	14.5
Hay fever	3	4	1	9.4	16.8	13.5			14.8
Vasomotor rhinitis	2	2	0	11.2	13.2	12.2			
Total	12	16	4 (1 fail.)	8.2	16.8	12.1	11.6	17.0	14.6
Active pulmonary tuberculosis	3	3	1 (1 fail.)	11.2	14.8	12.8			16.2
Chronic nephritis (uncomplicated)	3	7	0	7.0	14.0	9.9			
Pernicious anemia (stage of remission)	3	8	3	8.0	17.8	12.7	9.0	15.0	12.6
Secondary anemia	1	2	0	8.6	9.6	9.1			
Pneumonia	14	17	4	8.6	15.2	11.1	9.0	21.4	15.4
Pregnancy	21	33	0	8.4	12.6	11 2			

THE SIGNIFICANCE OF THE CIRCULATION TIME

The magnesium and calcium circulation time (arm-to-tongue time) represents the time required for the blood to travel the pathway from the antecubital vein to the tongue. The ether circulation time (arm-to-lung time) represents the time required for the ether to travel from the antecubital vein to the arterial capillaries of the lung. The lung-to-tongue time is the magnesium or calcium time minus the ether time. The arm-to-tongue time is a measure to the circulation as a whole. The arm-to-lung time is a rough measure of the functional capacity of the right ventricle (that is, its ability to maintain a normal blood velocity through its afferent and efferent vessels). The lung-to-tongue time represents in similar fashion the functional capacity of the left ventricle.

NORMAL INDIVIDUALS

Ninety-one men and women ranging in age from 19 to 70 years were tested (Table I). Excluded from the group were patients with cardiovascular disease, pulmonary or bronchial disease, as well as those with anemia or nephritis, and pregnant women, in whom circulation-time studies with agents other than magnesium have demonstrated departures from "normal."

The average circulation time was 12.9 seconds. The extremes were 7.0 to 17.8 seconds. One patient, perfectly normal in every way (with no evidence of myxedema or polycythemia), showed a reading of 19.8 seconds. Duplicate readings, taken on different days, rarely showed a variation exceeding two seconds. The circulation time is practically unrelated to weight, height, blood pressure, and pulse rate (within normal limits).

HEART DISEASE

The cardiac class numbered 126 and was divided almost equally between men and women. The ages ranged from 16 to 84 years. Two patients were in the ninth decade of life and 15 in the eighth decade. Included were 59 cases of hypertensive heart disease, 46 of arteriosclerotic heart disease, 6 of rheumatic heart disease, and 3 of syphilitic heart disease. A miscellaneous class comprised 2 cases of rheumatic fever (one with coarctation of the aorta), 1 of uncomplicated congenital heart disease, 4 of subacute bacterial endocarditis (3 with old rheumatic heart disease and 1 with congenital heart disease), 3 of thyrotoxic heart disease, and 2 of potential heart disease (electrocardiographic changes only).

There is no agreement in the literature concerning the relationship of the circulation time to the degree of heart failure. Some writers state that a direct proportionality exists between the circulation time and the degree of decompensation; others deny that such a relationship exists. Since no exact studies of this phase of the subject have hitherto been made, we grouped the cardiac patients in six classes

(Table II), under a classification easily adapted to clinical use, as follows: Compensated class, patients totally asymptomatic insofar as decompensation was concerned; Class A, only complaint exertional dyspnea; Class B, exertional dyspnea together with cyanosis; Class C, symptoms of Class A or B, or both, together with pulmonary congestion (as demonstrated by physical or roentgenologic examination); Class D, symptoms and signs of Classes A through C plus enlargement of the liver; Class E, symptoms and signs of Classes A through D plus dependent edema or ascites.

Although this classification may be open to criticism in certain exceptional cases, it is surprising how readily and how accurately cardiac patients may be fitted into one of the above classes by means of circulation-time studies.

Examination of Table III and Fig. 1 shows that as the degree of decompensation increases the circulation time increases steadily from the average of 13.0 seconds found in compensated cardiac patients, until, in Class E, it averages 30.3 seconds. The increase is sharpest in the transition from Class C to Class D and from Class D to Class E. The advent of exertional dyspnea in a cardiac patient is an important sign of approaching decompensation.

Ambulatory compensated patients with hypertension (Table II—Case 21) (Table III) showed a marked decrease of circulation time. That this decrease is not due to an increase in the basal metabolic rate, so often found in hypertension, is shown by the lack of correlation between decreases in the circulation time and such basal metabolic rates as were determined.

The presence of diabetes mellitus (Table II—Case 72) (Table III) seems to play no important role in the circulation time in hypertensive or arteriosclerotic heart disease.

Three patients had syphilitic heart disease, two with huge aneurysms (Table II—Case 97) (Table III). It is well to note the rapid circulation time of 17.8 seconds in a markedly decompensated patient (Table II—Case 226).

MYOCARDIAL INFARCTION, AURICULAR FIBRILLATION, ANGINA PECTORIS AND HEART BLOCK

The circulation time roughly parallels the degree of cardiac decompensation in rheumatic fever (Table II—Case 82) (Table III) and in subacute bacterial endocarditis (Table II—Case 60) (Table III). In congenital heart disease (Table II—Case 154) (Table III) the circulation time is often rapid.[2] The striking acceleration of the circulation time in hyperthyroidism (Table II—Case 90) (Table III) has been commented upon many times[13, 20, 36] and is worthy of mention as an important aid in the diagnosis of hyperthyroidism, especially in

obscure cases. It is noteworthy, also, that in patients with hyperthyroidism and cardiac failure the circulation time may fall well within normal limits (Table II—Case 62); in these cases it is the algebraic sum of the hyperthyroid circulation time and that usually expected in a corresponding degree of circulatory failure in patients with no hyperthyroidism.

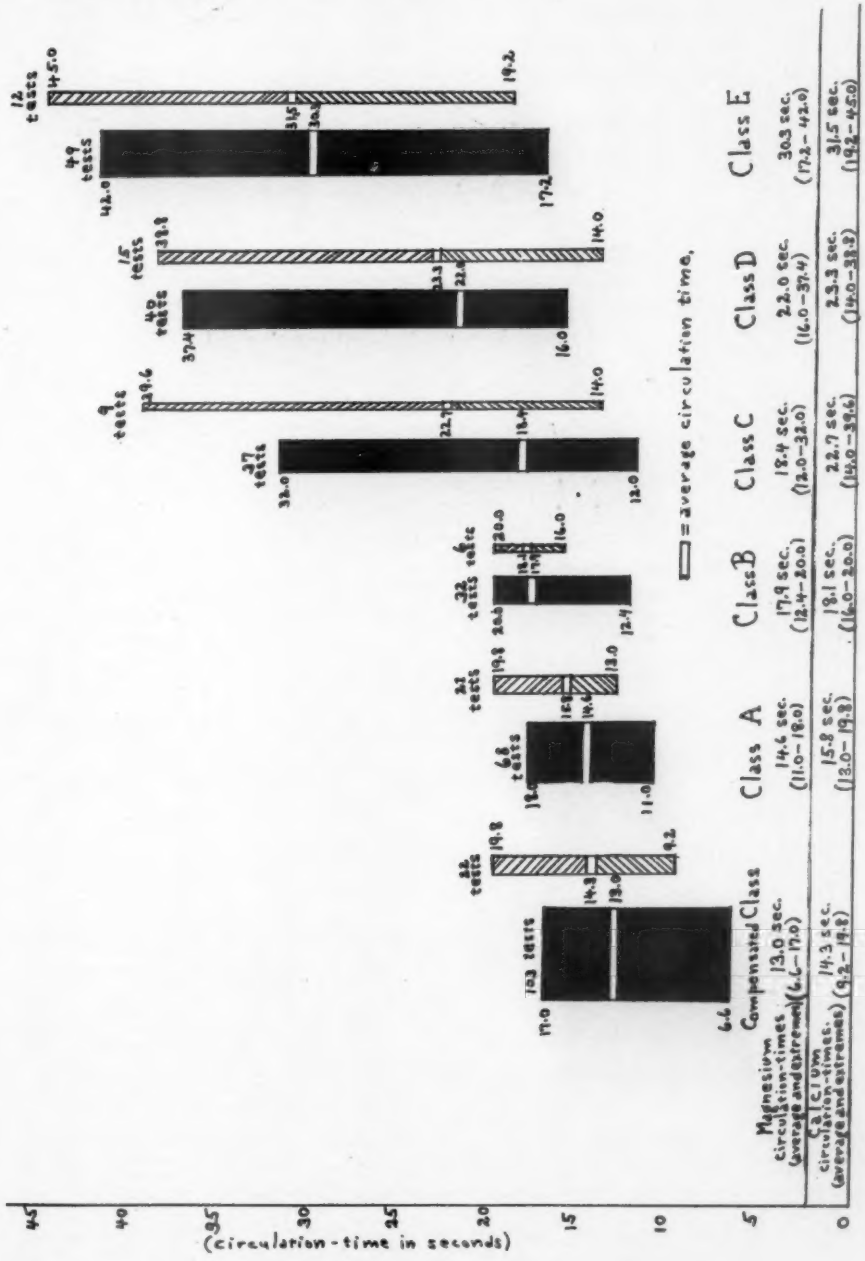

Fig. 1.—Magnesium sulfate and calcium gluconate circulation times in cardiac disease. (See footnote of Table II for explanation.)

TABLE

ILLUSTRATIVE MAGNESIUM SULFATE, CALCIUM GLUCONATE,

CASE NO.	NAME	AGE	SEX	BLOOD PRESSURE	STATUS ON ADMISSION	MAGNESIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	CALCIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	ETHER CIRCULATION TIME (ARM-TO LUNG TIME) (SEC.)	MAGNESIUM MINUS ETHER TIME (LUNG-TO-TONGUE TIME) (SEC.)
21	J. G.	40	M	180/100		11/9/37 9.8 (comp.) 11/15/37 10.4 (comp.) 12/17/37 8.4 (comp.) 12/31/37 10.4 (comp.)	11/9/37 16.0—faint end point 12/17/37 10.0—faint end point	11/9/37 8.4	11/9/37 1.4
72	F. G.	58	F	160/ 90	A	13.2 (A) (7) 13.4 (A) (13)	17.2 (7)	8.8 (7)	4.4 (7)
97	R. J.	60	F	164/ 74	A	13.8 (A) (5)	19.0 (5)	—	—
226	H. F.	55	M	154/ 34	E	17.8 (E) (62)	27.0 (62)	9.6 (62)	8.2 (62)
82	E. G.	22	F	200/110	Comp.	14.6 (comp.) (6) 15.6 (comp.) (6)	—	— 9.0 (6)	5.6 (6) 6.6 (6)
60	S. F.	19	M	100/ 60	B	20.0 (D) (15) 26.6 (D) (35) 19.0 (D) (23) 16.0 (D) (38)	23.0 (15)	No end point on several occasions	
154	R. P.	42	F	140/ 78	Comp.	9.8 (comp.) (6) 10.0 (comp.) (14) 9.4 (comp.) (8)	—	—	
90	S. H.	60	F	192/114	Comp.	6.6 (2)	—	—	
62	G. F.	46	F	144/ 84	C	20.0 (C) (6) 16.2 (B) (10)	26.0 (6) 16.0 (9) 16.0 (10)	10.0 (6)	10.0 (6)
231	M. M.	75	F	204/110	D	17.0 (D) (46)	14.0 (46)	5.0 (46)	12.0 (46)
223	L. W.	57	M	140/ 80	Comp.	24.8 (B) (6)	—	—	
131	A. M.	52	M	124/ 90	B	19.0 (B) (1)	—	—	

II

AND ETHER CIRCULATION TIMES IN CARDIAC DISEASE

CALCIUM MINUS ETHER TIME (LUNG-TO-TONGUE TIME) (SEC.)	ELECTROCARDIOGRAM	X-RAY	REMARKS
11/9/37 7.6	Normal		12/15/37 B.M.R. plus 27%. 2/ 9/38 B.M.R. plus 9%. Hypertensive heart disease. Ambulatory patient.
8.4 (7)	Arteriosclerotic heart disease		Hypertensive heart disease with diabetes mellitus.
—	Severe myocardial disease Marked left axis deviation	Heart enlargement	Ven. pres. (5) = 12.1 cm. saline solution; Wassermann, 4+. Necropsy: colloid goiter; aortic sac. aneurysm; toxic hyperplasia.
17.4 (62)	Arteriosclerotic heart disease	Heart greatly enlarged Aorta widened	Syphilitic heart disease; aortic regurgitation, aur. fibrillation; decomp., repeated paracent., thoracic and abdominal; Wassermann, 4+.
—	Myocardial changes consistent with congenital heart disease	Heart N/1 normal in size. Coarctation beginning of transverse aortic arch	Coarctation of aorta. Acute rheumatic fever.
	Right deviation; congenital heart disease		Congenital heart disease. Post-mortem examination showed pulmonic artery stenosis, patent foramen ovale, and subacute bacterial pulmonary arteritis.
	Normal		Patent ductus arteriosus. Pulmonary infarction.
	Slight myocardial changes		Masked hyperthyroidism; B.M.R. plus 31%. Ven. pres. = 7.8-11; 4 cm. saline; pulse 92.
16.0 (6)	Auricular fibrillation; severe myocardial disease; arborization block	Heart and lungs normal	Thyroid adenoma, cystic degeneration. Thyrotoxic myocardial degeneration. Aur. fibrillation. Died suddenly 9 days after operation.
9.0 (46)	Auricular fibrillation	Marked cardiac enlargement	Auricular fibrillation. Hypertensive heart disease.
	Auricular fibrillation Marked myocardial fibrosis		Thromboangiitis obliterans; aur. fibrillation. Arteriosclerotic heart disease.
	Myocardial disease		Severe angina pectoris. Died suddenly in anginal attack (2).

TABLE

CASE NO.	NAME	AGE	SEX	BLOOD PRESSURE	STATUS ON ADMISSION	MAGNESIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	CALCIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	ETHER CIRCULATION TIME (ARM-TO-LUNG TIME) (SEC.)	MAGNESIUM MINUS ETHER TIME (LUNG-TO-TONGUE TIME) (SEC.)
221	R. N.	17	M	94/ 60	E	30.0 (E) (35) 34.0 (E) (73) 33.0 (E) (127) 28.8 (E) (217)	40.0 (217) 42.0 (231)	22.0 (217)	6.8 (217)
65	M. G.	54	F	160/110	A	14.3 (A) (3) 12.2 (A) (16) 11.8 (A) (16) 13.4 (A) (4) 12.6 (A) (14)	14.8 (14)	6.0 (10)	6.2 (10)
162	G. R.	28	M	114/ 74	D	37.0 (D) (4) 27.6 (D) (5) 32.8 (D) (7) 28.2 (D) (12) 28.2 (D) (14) 42.0 (E) (18)	38.8 (4)	7.0 (4)	30.4 (4)

Compensated Class (Comp.)—No symptoms or signs of cardiac decompensation.
Class A—Exertional dyspnea.
Class B—Dyspnea and cyanosis.
Class C—Dyspnea, cyanosis, and pulmonary congestion.
Class D—Symptoms and signs of Classes A-C plus hepatic congestion.
Class E—Symptoms and signs of Classes A-D plus dependent edema or ascites.

NOTE:—Capital letters refer to cardiac status, as in above legend. Arabic numerals in parentheses refer to the day, after admission of the patient to the hospital, on which the circulation time was performed.

A group of 24 patients with myocardial infarction (Table II—Case 65), as outlined in Table III, showed no striking variations in circulation times from those obtained for the cardiac group as a whole.[24, 51] The utter lack of harmony between the circulation-time value in auricular fibrillation and the degree of decompensation was shown convincingly in 11 cases—3 of hypertensive heart disease, 3 of rheumatic heart disease, 4 of arteriosclerotic heart disease, and 1 of thyrotoxic heart disease (Table II—Cases 231, 223). The presence of angina pectoris had no effect per se on the circulation time in 7 cases—4 of hypertensive heart disease and 3 of arteriosclerotic heart disease. Magnesium may be used with apparent impunity in these patients. In fact, in one patient with an extreme form of angina pectoris (Table II—Case 131) death occurred suddenly in a severe anginal attack; yet the day previously a magnesium circulation-time test was performed without any reaction whatsoever. No definite relationship between the degree of heart block and the circulation time was noted in 7 cases of heart block—3 of first degree heart block, 2 of right bundle branch block, 1 of transient, almost complete, heart block following an attack of insulin hypoglycemia, and 1 of postscarlatinal heart block (Table II—Case 221[37]).

II—CONT'D

CALCIUM MINUS ETHER TIME (LUNG-TO-TONGUE TIME) (SEC.)	ELECTROCARDIOGRAM	X-RAY	REMARKS
18.0 (217)	Complete heart block; heart rate 32; pulse 32	Heart considerably enlarged	Complete heart block. Postscarlatinal myocarditis. Bilateral hydrothorax, marked enlargement of liver. Huge ascites.
9.8 (10)	Recent anterior coronary thrombosis		Acute infarction, day before admission. Hypertensive heart disease.
31.8 (4)	Severe myocardial disease Auricular fibrillation	Mitral stenotic lesion Heart enlarged	Aur. fibrillation. Post-mortem examination showed mitral stenosis and aortic regurgitation.

BRONCHIAL AND PULMONARY DISEASES

The difficulty of diagnosing cardiac failure with certainty in the presence of pulmonary emphysema offers a baffling clinical problem. The cardinal symptoms—exertional dyspnea, cyanosis, cough, and often dependent edema—are present in both pulmonary emphysema and cardiac failure.[38, 16] In the differentiation of the two conditions, even electrocardiograms and orthodiagrams may be misleading. The circulation time may be of considerable value here. If rapid, it indicates that the heart is well compensated and is playing no role in the production of the symptoms; if of average duration or of high normal value, it does not necessarily exclude the possibility that heart failure is either primarily responsible for the symptoms or shares the responsibility with the pulmonary emphysema. In our series there were 5 cases of both pulmonary emphysema and arteriosclerotic heart disease (1 patient had bronchiectasis, as well), in which the circulation time matched the cardiac condition rather than the pulmonary. In two additional cases of heart disease and bronchial asthma, cardiac decompensation was excluded by the rapid circulation times obtained.

The accelerated circulation times obtained in 7 cases of bronchial asthma are in accord with other reports.[20] In the differentiation of bronchial asthma and so-called cardiac asthma the remarks in the preceding paragraph apply with equal force. No striking aberrations were obtained in pneumonia (6 lobar and 8 bronchopneumonia) or active pulmonary tuberculosis.[53]

TABLE
DETAILED ANALYSIS OF
CIRCULATION TIME

DIAGNOSIS	TOTAL			COMPENSATED CLASS				CLASS A			
				MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM	
	NO. OF PATIENTS	NO. OF TESTS		NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)
		MAG.	CALC.								
Uncomplicated hypertension cases											
A—Ward	19	39	5	8	14.4 (9.4-17.0)	1	— (19.8)	9	13.4 (11.0-16.2)	2	17.9 (16.0-19.8)
B—Outpatient	18	61 1 fail.	18 1 fail.	32	11.5 (8.2-15.0)	9	12.1 (9.2-16.0)	26	14.8 (11.0-18.6)	8	15.2 (12.0-19.6)
Hypertension with diabetes mellitus	10	31	8	15	14.5 (11.4-17.0)	4	15.3 (13.0-19.8)	2	13.3 (13.2-13.4)	1	— (17.2)
Arteriosclerotic heart disease	34	69	7	22	13.7 (11.2-16.2)	5	16.1 (12.0-20.0)	10	17.3 (14.0-18.6)	1	— (19.8)
Myocardial infarction											
A—Hypertension	9	22	7	5	14.2 (13.0-16.0)	—	—	10	13.5 (12.0-16.8)	4	14.9 (13.0-16.0)
B—Hypertension and diabetes mellitus	3	4	0	—	—	—	—	—	—	—	—
C—Arteriosclerotic heart disease	12	30	22	8	12.5 (10.8-15.0)	3 1 fail.	15.1 (12.4-17.0)	4	15.6 (14.4-18.0)	3	16.3 (15.0-18.0)
Total (myocardial infarction)	24	56	29 1 fail.	13	13.1 (10.8-16.0)	3 1 fail.	15.1 (12.4-17.0)	14	14.1 (12.0-18.0)	7	15.5 (13.0-18.0)
Rheumatic heart disease	6	46	10	1	— (10.0)	—	—	—	—	—	—
Rheumatic fever (coarctation of aorta)	2	3	0	1	— (12.0)	—	—	2	15.1 (14.6-15.6)	—	—
Syphilitic heart disease	3	3	2 1 fail.	1	— (16.6)	1 fail.	—	1	— (13.8)	1	— (19.0)
Congenital heart disease and subacute bacterial endocarditis	5	12	2	4	11.1 (9.4-15.0)	—	—	4	11.7 (9.0-13.0)	1	— (16.0)
Thyrotoxic heart disease	3	5	3	3	9.9 (6.6-12.2)	—	—	—	—	—	—
Potential heart disease (EKG. changes)	2	3	—	3	12.0 (12.0)	—	—	—	—	—	—
Summary	126	329 1 fail.	85 3 fail.	103 1 fail.	13.0 (6.6-17.0)	22 3 fail.	14.3 (9.2-19.8)	68	14.6 (11.0-18.0)	21	15.8 (13.0-19.8)

*See footnote of Table II for explanation.

TABLE III

MAGNESIUM AND CALCIUM IN CARDIAC GROUP*

CLASS B				CLASS C				CLASS D				CLASS E			
MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM	
NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)	NO. OF TESTS	AV. AND EXTREMES (SEC.)
4	17.5 (12.4-19.4)	1	— (17.6)	8	17.5 (12.0-25.0)	—	—	8	21.7 (17.0-23.8)	1	— (14.0)	2	30.3 (21.0-39.6)	—	—
1	— (18.6)	—	—	1	— (21.0)	1	— (39.6)	—	—	—	—	—	—	—	—
6	16.1 (14.2-20.0)	—	—	—	—	—	—	2	17.0 (16.0-18.0)	2	22.7 (22.6-22.8)	6	24.3 (21.4-27.2)	1	— (29.6)
11	20.1 (16.0-24.8)	—	—	14	21.0 (16.0-32.0)	—	—	11	20.8 (17.0-28.0)	—	—	1	— (17.8)	1	— (27.0)
2	16.7 (16.2-17.2)	1	— (20.0)	5	17.7 (15.2-23.0)	1	— (24.0)	—	—	1	— (27.8)	—	—	—	—
1	— (14.0)	—	—	2	12.3 (12.0-12.6)	—	—	1	— (19.0)	—	—	—	—	—	—
6	21.5 (17.0-26.2)	1	— (19.0)	6	20.8 (15.0-32.0)	6	14.1 (14.0-19.8)	8	20.3 (16.0-24.6)	9	22.3 (16.0-35.0)	—	—	—	—
9	20.3 (16.2-26.2)	2	19.5 (19.0-20.0)	13	18.3 (12.0-32.0)	7	19.8 (14.0-24.0)	9	20.1 (16.0-24.6)	10	22.9 (16.0-35.0)	—	—	—	—
—	—	—	—	—	—	—	—	6	29.9 (25.2-37.4)	1	— (38.8)	39	31.7 (17.2-42.0)	9	32.8 (19.2-45.0)
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	1	— (17.8)	1	— (27.0)
—	—	—	—	—	—	—	—	4	20.4 (16.0-26.6)	1	— (23.0)	—	—	—	—
1	— (16.2)	2	16.0 (16.0)	1	— (20.0)	1	— (26.0)	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
32	17.9 (12.4-20.0)	6	18.1 (16.0-20.0)	37	18.4 (12.0-32.0)	9	22.7 (14.0-39.6)	40	22.0 (16.0-37.4)	15	23.3 (14.0-38.8)	49	30.3 (17.2-42.0)	12	31.5 (19.2-45.0)

MISCELLANEOUS CLINICAL CONDITIONS

Normal readings were obtained in small groups of cases of cholelithiasis, nephroptosis, uncomplicated diabetes mellitus, and pernicious anemia in the stage of remission. One patient with marked secondary anemia showed rapid circulation times.[39] Six patients with chronic glomerulonephritis, 3 uncomplicated and 3 with myocardial disease, showed nothing striking in circulation-time studies. No toxic effects were observed.[40]

In 5 patients with enlargement of the liver due to portal cirrhosis, arsphenamine hepatitis, or secondary carcinoma, the circulation times were normal. Jaundice is no deterrent to the use of the test; when it is present the circulation time may be of great value in differentiating enlargement of the liver due to cardiac from that due to extracardiac disease.

PREGNANCY

In 21 cases of pregnancy, nearly all of which were studied just prior to active labor, there was a marked increase in blood velocity, which is a clear indication of the burden pregnancy places upon the circulation. It is surprising to find that work done with other circulation-time agents indicated a slight but progressive retardation of blood flow in pregnancy.[22]

COMPARISON OF MAGNESIUM AND CALCIUM AS CIRCULATION-TIME AGENTS

A glance at Table II shows numerous discrepancies between the magnesium and calcium arm-to-tongue circulation times in the same individual. Table III and Fig. 1 sum up the differences. Almost invariably the calcium time was longer. The reaction with magnesium is extremely sharp, so sharp in many cases as to afford an objective, as well as subjective, reaction. In the normal group the differences are not so marked except in a few cases (the calcium time ranging from eight-tenths to eight seconds longer than the corresponding magnesium time). In the cardiac groups the differences were more pronounced, being accentuated, in a general way, as the degree of decompensation increased. The discrepancies often ran as high as twelve to fifteen seconds. Therefore, especially in classes A and B, in which the diagnosis of cardiac decompensation is so often difficult to make clinically, the abnormally long calcium lung-to-tongue times may lead to erroneous diagnoses of left-sided heart failure.

The empirical fear of most clinicians of intravenous calcium therapy has recently been amply substantiated, both in reports on human beings[41, 54] and in animal experiments.[42-46] Electrocardiographic studies of the normal human heart show in a large percentage of subjects marked changes in the T- and P-waves, as well as occasional cardiac

arrest.[35] Similar studies, following calcium intravenously, in cases of heart disease are not available. There can be very little question of the toxic effects from the combined use of calcium and digitalis. Changes in the heart rate after therapeutic doses of calcium, ventricular fibrillation after toxic doses, and even sudden fatalities in patients who received calcium intravenously after previous administrations of digitalis have been reported.[47]

"Study indicates the hazard existing in the use of calcium gluconate intravenously following digitalis. . . . The conclusion is reached that great caution is to be used in giving calcium intravenously with or shortly after digitalis. It is apparently not safe to use this combination in patients who have received small doses of digitalis."[42]

All observers are in accord that *calcium must be injected slowly* to minimize its toxic effects.[35, 48] And yet, when used as a circulation-time agent, calcium must be injected as rapidly as possible. In the present series, an intravenous injection of calcium hastened the death within a few hours of a patient who had been digitalized and was in fairly good condition prior to the injection. A few years ago the junior author had a similar experience with a digitalized hypertensive patient who was given an intravenous calcium injection after a cholecystectomy and died suddenly during the course of the injection (case unreported).

On the other hand, the intravenous injection of magnesium has no deleterious action on the heart. A study of 100 patients, of whom many were seriously ill cardiac patients, with electrocardiographic tracings taken concurrently with the magnesium injections, revealed no evidence of myocardial damage.* In many of these patients, 10 to 20 c.c. of a 10 per cent solution of magnesium sulfate were injected rapidly with no ill effects. Practically all patients with decompensation received digitalis both orally and parenterally, many up to the point of complete digitalization, with no toxic effects.

A surprising feature in our experience was the occurrence of 7 failures and 1 partial failure (the patient feeling the heat sensation in the back only, 40 seconds after the beginning of the injection) in 123 calcium injections. It is curious that no mention of such failures has been made by other authors. In the magnesium group (579 tests) there was 1 failure (a young patient with hypertension who reacted normally in subsequent tests).

CRITERIA

Magnesium sulfate fulfills well the criteria proposed for the ideal circulation-time agent. It is nontoxic in the dose employed. It does not influence blood velocity until the end reaction has occurred—this despite the fact that in many patients with hypertension and in some

*Detailed report to be published subsequently.

without hypertension a sharp fall of both diastolic and systolic pressure occurs immediately after an injection. That this change in blood pressure is compensated for by the circulatory mechanism is attested by the fact that circulation times, repeated within two or three minutes, show almost duplicate values. Accidental paravenous infiltration produces no pain, venous thrombosis, or slough. The magnesium is eliminated rapidly through the kidneys. The end reaction is readily discernible in normal and pathologic conditions and is so sharp that the test in many patients becomes practically objective as well as subjective. And lastly, the cost of the reagent (chemically pure magnesium sulfate) is practically negligible; it is possible to prepare large autoclaved quantities in ampoule vials so cheaply that the general practitioner has at his command, for bedside or office use, a valuable, easily applied addition to his diagnostic armamentarium.

TABLE IV

ETHER CIRCULATION TIME*

(Fifty-Six Noncardiac Patients; Forty Cardiac Patients)

NO. OF TESTS	ETHER TIME (ARM-TO-LUNG TIME) (SEC.)	MAGNESIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)	CALCIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)	NO. OF TESTS	ETHER TIME (ARM-TO-LUNG TIME) (SEC.)	MAGNESIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)	CALCIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)
Noncardiac Class				*Compensated Cardiac Class*			
80	5.7 (2.6-9.0) 1 test = 10.0	5.1 (2.2-10.8)	7.6 (3.4-12.2)	14	7.3 (5.0-10.0)	5.8 (2.4-9.2)	8.3 (6.0-11.4)
Class A				*Classes B to E*			
14	6.7 (5.2-9.6)	6.3 (2.4-11.0)	8.8 (3.4-11.8)	28 (1 fail.)	— (5.0-22.0)	— (2.6-30.4)	— (11.8-31.8)

*See footnote of Table II for explanation.

THE ETHER CIRCULATION TIME AND LUNG-TO-TONGUE TIME

The ether times in the noncardiac group and in the compensated and Class A groups of the cardiac series were approximately equal (Table IV). In the other cardiac groups the ether time was either normal or greatly prolonged, depending on whether the functional integrity of the right heart was intact or impaired. In one case (Table II—Case 60) of congenital heart disease with a superimposed subacute bacterial pulmonary arteritis, repeated trials failed to produce an ether end point. The magnesium lung-to-tongue time was appreciably shorter than the calcium lung-to-tongue time on account of the correspondingly smaller values for the magnesium arm-to-tongue time.

DISCUSSION

The circulation time is of greatest clinical interest in cardiac decompensation, the condition par excellence in which a slowing of the blood velocity occurs. As has been shown, it is the status of the circulation, irrespective of the etiological factors or mechanical status of the heart, that determines the blood velocity. The presence of heart disease per se, irrespective of etiology, does not influence the blood velocity. Likewise, the presence of such mechanical factors as auricular fibrillation or mitral stenosis plays no important role. It is only when decompensation occurs that the circulation time changes. A detailed analysis of our results shows clearly that the circulation time is *not* the infallible diagnostic tool it was originally believed to be. A rapid circulation time (excluding the presence of uncomplicated hyperthyroidism, marked anemia, or high fever) excludes cardiac decompensation. However, much more common than has been believed is the occurrence of normal circulation times in markedly decompensated patients. In general, as the degree of decompensation increases, the circulation time increases, but not in strict proportionality, so that the absolute value of the individual test does not necessarily reflect the clinical status in any case. More important than the absolute value of the circulation time in any individual is the change in circulation time from time to time in that individual. This is well illustrated by Table II—Case 162; the patient's rapid change for the worse, at the end, was heralded by a corresponding increase in the circulation time. In this respect, as a teleologic agent, the test is of great value.

The test may also be of importance in separating edema and ascites of cardiac origin from that of extracardiac origin. Of similar import is its use in noncardiac hepatomegalies.

The results obtained demonstrate conclusively that magnesium is preferable to calcium as an agent in the determination of the circulation time. This holds true because of its sharpness of reaction and shorter reaction time, lack of deleterious action on the heart, and dependability.

CONCLUSIONS

1. The use of a 10 per cent solution of magnesium sulfate as an agent for the determination of the circulation time is described. Five hundred seventy-nine magnesium sulfate tests were performed in 274 patients, of whom 126 were cardiac and 146 noncardiac patients. As a check, 123 calcium gluconate circulation-time tests, as well as 137 ether tests, were performed.

2. The technique of the test is presented in detail.

3. In 91 "normal" subjects, representing a wide diversity of noncardiac conditions, the average circulation time was 12.9 seconds. The extremes were 7.0 and 17.8 seconds.

4. In the cardiac group, the ages ranged from 16 to 84 years; 2 patients were in the ninth decade of life and 15 in the eighth decade.

5. The cardiac group included 59 cases of hypertensive heart disease, 46 of arteriosclerotic heart disease, 6 of rheumatic heart disease, and 3 of syphilitic heart disease. A miscellaneous group comprised 2 cases of rheumatic fever (one with coaretation of the aorta), 1 of uncomplicated congenital heart disease, 4 of subacute bacterial endocarditis (3 with old rheumatic heart disease and 1 with congenital heart disease), 3 of thyrotoxic heart disease, and 2 of potential heart disease.

6. The cardiac group was divided into six classes, varying in the degree of compensation, under a classification easily adapted to clinical use. A detailed correlation of the circulation tests with this grouping establishes the fact that, as a whole, the circulation time increases steadily as the degree of decompensation increases, but that there is no strict proportionality between the circulation time and the degree of decompensation.

7. Ambulatory compensated patients with hypertension have a rapid blood velocity.

8. Diabetes mellitus per se has no effect on the circulation time.

9. The blood velocity is determined to a great extent by the status of the circulation, irrespective of the etiological factors involved, such as hypertensive, arteriosclerotic, rheumatic, or syphilitic heart disease, or the presence of mechanical factors, such as auricular fibrillation.

10. The presence of a high normal circulation time is common in advanced degrees of cardiac decompensation. Consequently, the circulation time is of limited value in the diagnosis of cardiac decompensation.

11. The change in blood velocity from time to time in the same patient is of much more importance than the absolute value of the circulation time, and may be of great teleologic importance.

12. Magnesium sulfate is totally innocuous in angina pectoris, heart block, myocardial infarction and nephritis.

13. It may be of help, within certain limits, in differentiating pulmonary emphysema and myocardial failure, as well as bronchial asthma and cardiac asthma. It may be of value also in separating hepatomegaly of cardiac origin from that of extracardiac origin. The test may be used safely in the presence of jaundice.

14. The circulation time is rapid in hyperthyroidism, pneumonia, marked anemia, and pregnancy. It is normal in active pulmonary tuberculosis and normal or somewhat rapid in bronchial asthma.

15. Conclusive evidence is given of the marked superiority of magnesium over calcium as a circulation-time agent.

16. The intravenous injection of magnesium has no deleterious effect on the heart, as shown by electrocardiographic tracings made on 100

patients during the injection. The magnesium circulation test is harmless in digitalized patients.

17. The ether time in normal subjects and in cardiac patients with incipient decompensation is normal, averaging 5.7 seconds, with extremes from 2.6 to 10 seconds. The ether time is increased in right-sided heart failure, and the lung-to-tongue time (magnesium circulation time minus ether time) is increased in left-sided heart failure.

18. The magnesium sulfate circulation test is well adapted for bedside and office use, thus affording a valuable diagnostic aid for the general practitioner.

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Department of Clinical Reports

GLOMUS TUMOR

Report of a Case

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ALTHOUGH Masson[1] first presented a histopathologic conception of glomus tumors as early as 1924, and although numerous authentic cases have, since then, been reported in the foreign literature,[2] it was not until 1934 that the first case report appeared in the American literature.[3] Lesions clinically identical with glomus tumor have been described under various headings, such as hemangioma, subungual tumors, and exostoses, etc., since 1812.[4] Up to the time our patient was first seen (August, 1936), there were about seventy cases on record.[5-15] With advancement in knowledge of the subject, the diagnosis has become much more obvious, and there has naturally been a relative increase in the number of cases reported. We wish to add ours to this group, particularly as we had the opportunity to observe the patient over a period of eighteen months after operation.

Because of the scarcity of reports of this tumor, it seemed desirable to present a brief general description of the histologic structure of the glomus itself before reporting the present case. A glomus is a specialized arteriovenous anastomosis.[16] It may appear almost anywhere over the cutaneous surfaces of the body and in the subungual regions, but is by far most frequently encountered in the extremities. Depending on the location, a glomus may vary in width from 60 to 220 microns. The glomus undergoes considerable alteration with age. It is formed imperfectly at birth, reaches maximum development in young adult life, and atrophies in old age. It is distributed widely among other mammals in much the same regions as in man. A significant fact is that the glomus has not been described in cold-blooded animals, yet it is very prominent in birds whose body temperature is above that of mammals.

The cutaneous glomus occupies a specific zone of the cutis—the stratum reticulare. Briefly, it consists of the following: an afferent artery, carrying blood from the interior of the body; a canal called the Suquet-Hoyer canal, connecting the artery with the vein; preglomic arterioles nourishing all the constituents of the glomus; a clear periglomic zone or expansion zone furnished with a neuroreticular

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mechanism which controls the function of the Suquet-Hoyer canal; a specially arranged system of collecting veins; and an outer lamellated collagenous zone surrounding the entire glomus. Collecting venules are provided with septa or valves, and each channel communicates with that of the main collecting vein (Fig. 1). The cutaneous glomus is so named because of its similarity to the glomus coccygeum and its homologues.

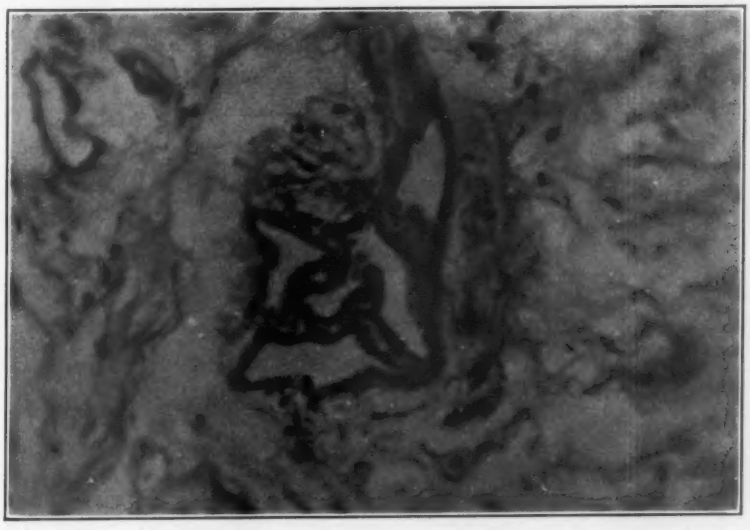

Fig. 1.—Cross section showing the septa or valves in the venules. Hematoxylin and eosin stain (×200).

CASE REPORT

History.—Mr. R., an executive, aged thirty-eight years, had noticed a purple-bluish spot under the lower inner corner of the nail of the left index finger for fifteen to twenty years previous to his examination on Aug. 14, 1936. During this time he had suffered paroxysms of shooting pain in the tip of the finger, radiating to the forearm and arm and occasionally reaching the shoulder. The pain was markedly aggravated by cold weather and relieved by warm weather or by immersion of the finger in hot water. The slightest pressure exerted over the purple-bluish spot evoked excruciating pain. In recent years the condition had become much more painful. There had been no increase in size of the tumor area with passage of time under normal conditions, nor did it enlarge during the paroxysmal attacks. All sorts of therapy, including superficial curettement, had been employed without improvement. There was no history of trauma. The patient was a total abstainer from tobacco and drank only occasionally. The past history was otherwise entirely negative.

Examination showed a purple-bluish discoloration about one-fourth of an inch in its longitudinal diameter, located under the lower inner corner of the nail of the left index finger. There were no thermal changes and a detailed study of the nail fold capillaries did not reveal any abnormalities. A roentgenogram of the finger failed to show an area of depression in the bone or other evidence of pathologic change. Pressure over the tumor area or immersion of the finger in ice-cold water produced excruciating pain.

Fig. 2.

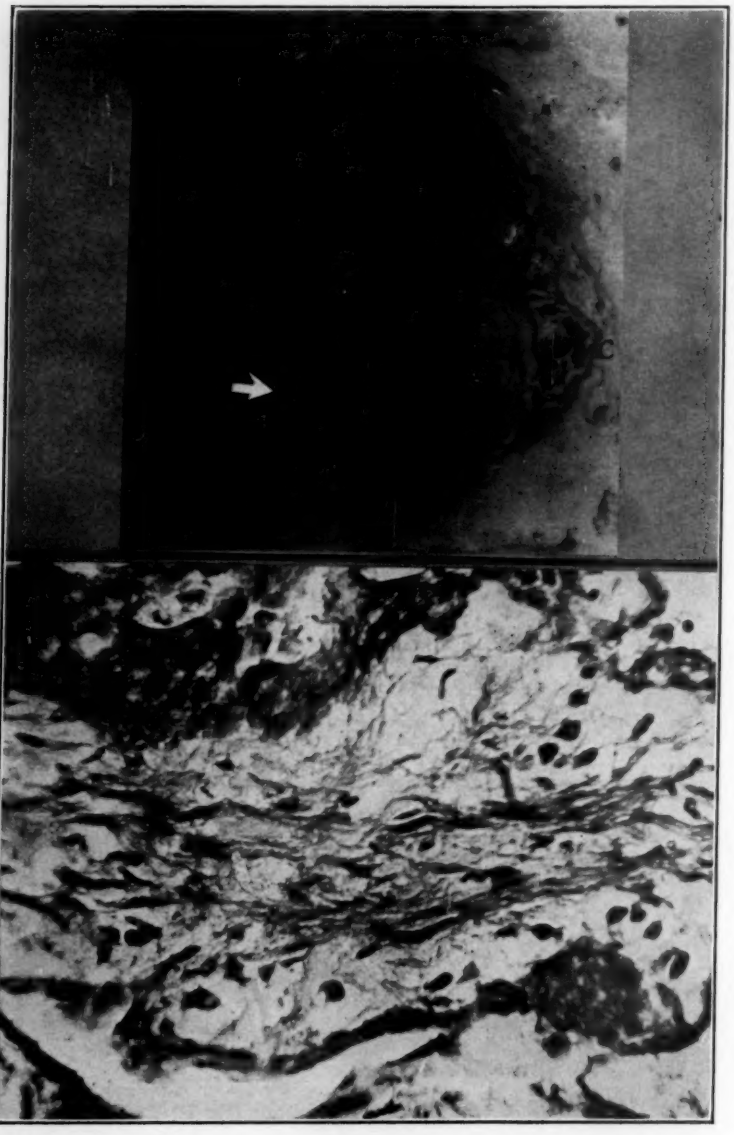

Fig. 3.

Fig. 2.—Cross section through entire tumor mass showing the sinusoidal canals. The artery can be seen in the tumor, while the collecting vein is seen at its edge. *A*, artery; *B*, sinusoidal canal; *C*, collecting vein. Hematoxylin and eosin stains (×160).

Fig. 3.—Nerve fibers running between masses of tumor cells. A blood vessel lined with swollen endothelial cells is seen at the lower part of the section. Weigert's stain (×1600).

Course.—The patient was operated on by Dr. Louis R. Davidson at the New York Post Graduate Hospital Oct. 7, 1936. Under block anesthesia with 2 per cent novocain, the ulnar aspect of the nail bed and the matrix were removed with the glomus tumor and two interrupted sutures were employed distally and proximally for hemostasis. Black silk suture material was used for the skin. Local pain was present for several days after operation, and healing was complete in one week.

Pathology.—This study was carried out and reported as follows by Dr. Louise H. Meeker. *Gross examination* indicated the specimen measured 28 by 18 by 8 mm. One surface was covered by a portion of nail, about which there were a few millimeters of skin. The nail bed was included, and beneath the bluish area seen in the nail there was a small bluish circumscribed area a few millimeters in diameter, somewhat different in appearance from the surrounding fibrous tissue. On *microscopic examination* stained sections showed a central area formed of ramifying sinusoidal canals (as in cavernous hemangiomata), separated by bands of epithelioid cells which were supported by strands of collagen fibers (Fig. 2). Between the epithelioid cells were strands of nonmedullated nerve fibers which were easily demonstrated by special nerve tissue stains, such as Weigert's (Fig. 3). The epithelioid cells were much more numerous than the other tissues. They formed wide mantels over the septa between the vascular channels. The epithelioid character of the cells was emphasized by the formation of cell bridges. Surrounding this central area was a layer of connective tissue, forming a pseudocapsule in which arterioles and small veins were scattered.

COMMENT

Glomus tumors are benign arterial neuromyomatous lesions of the glomus, a structure normally present in man and warm-blooded mammals. The history of the existence of a purple-bluish or reddish area of discoloration, commonly located under the nail bed but sometimes found elsewhere, which has been present for a long time and is associated with characteristic paroxysms of local pain, makes the clinical diagnosis readily apparent.

SUMMARY

The case of a patient with a glomus tumor is presented. Examination eighteen months subsequent to complete surgical removal shows apparently permanent recovery. This result confirms those obtained in all cases previously reported. Once the diagnosis has been established, immediate surgical removal is advised.

I wish to express my appreciation to Dr. A. Wilbur Duryee and Dr. Irving S. Wright who aided in the diagnosis and study of this case.

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PULMONARY CONUS STENOSIS WITH CLOSED FETAL PASSAGES*

Report of a Case

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THE following report describes a third case of pulmonary conus stenosis with closed fetal passages. The first two were reported by Eakin and Abbott[1] and by Abbott.[2]

While the principal structure of the heart to be described is practically the same as in at least one of the cases mentioned, secondary changes and the remarkable duration of life (65 years) seem to warrant this report.

REPORT OF CASE

A 65-year-old, white, married woman came to the Worcester City Hospital, Jan. 13, 1937, complaining of pain in the chest and shortness of breath. She had been in bed practically ever since her previous admission nine weeks before. It was found that she had had several hospital admissions which may be summarized as follows:

Feb. 20, 1933, she was admitted with the diagnosis of grippe. She had felt poorly for a month, with easy fatigability, weakness, palpitation, and cough. These symptoms culminated in her admission to the hospital.

Her past history showed that she had had rheumatic fever at the age of 17 years, since which time she had been known to have "heart disease." She had pneumonia at the age of 34 years. There had been no other illness of note.

The family history was not contributory. She had been married forty-three years and her husband was living and well at the time of her admission. She had one daughter who was in good health at the age of 42 years.

Physical examination was reported as showing a well-developed and nourished white woman. The positive findings were coarse, moist râles at the bases of both lungs, especially the right, with moderate dullness and diminished breath sounds over these areas. The heart was not thought to be enlarged. The sounds were of good quality. The rhythm was normal. There was a loud blowing systolic murmur in the mitral area which was transmitted to the left axilla and heard with less intensity at the aortic and pulmonary areas. The blood pressure was 160/60. The diagnosis at this time was rheumatic heart disease with mitral regurgitation and mild congestive heart failure.

At this admission she was found to have strongly positive blood Hinton and Kahn reactions. Roentgenologic examination showed a very large heart with the apex reaching the left axilla; atheroma was demonstrated in the widened aorta.

There were several subsequent admissions, the only new development being an aortic diastolic murmur. Of chief interest are the various diagnoses made by the different examiners. These were chiefly as follows: arteriosclerotic heart disease with congestive heart failure; syphilis; aneurysm of the aorta; aortic stenosis. At one time one of us left the following note: "probably a calcareous aortic stenosis (with rough basal systolic murmur and thrill)." Some months later our opinion

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seems to have changed, for we suggest the possibility of congenital heart disease with a patent interventricular septum and an associated syphilitic aortic regurgitation.

Suffice it to say that her final admission occurred on Jan. 13, 1937. During this visit her congestive failure increased regardless of the usual cardiac therapy, and she died Feb. 26, 1937.

Necropsy.—Owing to limitations in the autopsy permission, only a part of the heart was retained, and examination of other organs consisted of inspection only.

The body was that of a well-developed, obese, elderly, white woman, 61.5 inches (153.8 cm.) tall, and weighing 141 pounds (64.1 kg.). The hair was gray. The teeth were in poor condition. There were old striae over the lower abdomen and the upper parts of both thighs. There was marked edema extending from the feet and ankles upward to, and including, the abdominal wall. There was no clubbing of the fingers or toes.

The pericardial cavity was completely obliterated by rather firm, extensive adhesions necessitating the removal of the heart and the pericardium *in toto* by sharp dissection from the surrounding structures.

The heart weighed 530 gm. (from the gross weight of 580 gm., a deduction of 50 gm. was made for adherent pericardium and extrapericardial fat). The coronary arteries showed slight to moderate infiltration with yellow intimal plaques. The walls of all chambers were of good brown-red color, except for a few irregular patches of shiny gray in the lining of both ventricles. The consistency of the myocardium was good. The left ventricle was markedly hypertrophied; its wall measured 2.6 cm. in thickness, while the right ventricle was only slightly hypertrophied, with a wall measuring 0.6 cm. in thickness. The tricuspid valve measured 11 cm. in circumference, the pulmonic 8.5 cm., and the mitral 9.5 cm. All of them were thin and smooth. The leaflets of the pulmonic valve carried thin, long fringes on their corpora arantii. The leaflets of the aortic valve were thickened and contained indurated, partly calcified nodules, but showed no fresh vegetations. They were partly fused with each other, resulting in a decrease of the circumference of the aortic valve to 4 cm. (calcareous aortic stenosis).

The left auricle showed nothing remarkable. The left ventricle, besides the muscular hypertrophy, showed an aneurysm-like pouch extending from the aortic vestibule towards the anterior leaflet of the tricuspid valve (Fig. 1). The entrance to this pouch was oval, measured 0.8 by 0.6 cm., and was located 1.1 cm. below the free edge of the aortic valve. The body of this pouch was slightly wider than its entrance and was lined by several thin, fibrous ridges. Its floor was located 0.5 cm. from the entrance, was found to be flush with the corresponding part of the tricuspid valve, and was smooth and extremely thin. On the right side of the heart, the pouch was located about 0.4 cm. above the attachment of the tricuspid valve, in the auricle. The right auricle was markedly dilated. The foramen ovale was closed.

The right ventricle was subdivided into two separate chambers. One of these chambers was located near the apex of the heart, without quite reaching it, and comprised what may be called the body of the right ventricle. The second chamber was located to the left of, and above, the first. It gradually tapered down from the size of the ventricular body to that of the pulmonary artery. However, a continuation of this second chamber consisted of a pyramidal, muscular structure on the anterior aspect of the heart, extending its lumen 4 cm. towards the right auricular appendage and touching it without communication.

The two chambers were separated by a transverse, fibromuscular septum located about 3 cm. below the attachment of the pulmonic valve (Fig. 2). The periphery of the septum consisted of thick muscles continuous with those of the ventricular wall. Its center was formed by a fibrous plate measuring about 1.5 cm. in diameter

and continuous with one leaflet of the tricuspid valve, with a perforation in the middle. The perforation was an oval, almost slitlike opening which admitted the tip of the little finger and measured 3 cm. in circumference (diameters: 1.3 and 0.8 cm.). Its free edges were thin and beset with thin fringes similar to those found at the pulmonary cusps; some were as long as 0.4 cm. The wall of the ventricular body (first chamber) showed thick trabeculae carneae and a normal moderator band. Apparently there was thickening, in patches, of the endocardium throughout this chamber. The upper chamber showed a smooth, grayish-brown lining uninterrupted by muscular ridges in its main part, but showing a few muscular elevations in its continuation described.

Fig. 1.—Looking down on aortic valve showing deformity of aortic leaflets and sealed interventricular defect and aneurysm.

The aorta showed little, if any, dextroposition. The thoracic portion had a circumference of 9 cm. in the ascending part, of 7 cm. in the arch, and of 6 cm. in the descending part. It showed marked infiltration with yellow intimal plaques and some calcification. Several areas showed patchy separation of calcified portions. Vestiges of the ductus arteriosus were not found, nor any anomaly of the branches of aorta or pulmonary artery.

Anatomic diagnosis was as follows: Pulmonary conus stenosis with closed fetal passages, congenital; calcareous aortic stenosis; acute adhesive pericarditis; aneurysm of membranous portions of interventricular septum; arteriosclerosis of aorta, marked, of coronary arteries, slight; peripheral edema.

Fig. 2.—View from apex of right ventricle showing stenosis of the pulmonary conus from below.

DISCUSSION

From the standpoint of purely descriptive anatomy, this is an example of constriction of the right ventricle by an incomplete transverse fibromuscular septum. As it obstructed the blood stream directed toward the pulmonary valve, it may be called a subpulmonary stenosis, in analogy to subaortic stenosis, both conditions being of no apparent vital importance unless they are extremely marked or complicated by other cardiac lesions.

Consideration of the homology of this abnormal structure leads one to a normally insignificant feature of the right ventricle, the crista supraventricularis. This is a ridge which marks off the conus arteriosus on the inner wall of the right ventricle. Ontogenetically, it corresponds to a constriction which, in the fourth and fifth weeks of embryonal life, separates the bulbus cordis from the common ventricle.

In our specimen, which is similar to the two referred to above, the upper chamber corresponds to the conus arteriosus in size, location, and the smooth appearance of its lining, whereas the lower chamber is characterized, as is the body of the ventricle, by its muscular relief.

It therefore seems to be obvious that the perforated intraventricular septum represents an arrest of the normal regression of an early embryonal structure to its vestige, the crista supraventricularis. This arrest results in what Eakins and Abbott call, very appropriately, pulmonary conus stenosis. As in their cases, so in ours, the formation of the interventricular septum had been completed, in contrast to the defect of the interventricular wall usually found in pulmonary conus stenosis. As a result of the complete closure of the entire cardiac system of fetal passages, all blood has to pass through the stenotic lower orifice of the conus. However, the relatively moderate size of this opening in our case seems to be the reason for the slight pulmonary congestion and the failure of the systemic circulation. It also explains why this patient lived a fairly normal life until her seventh decade, when the secondary diseases of the left side of the heart and the adhesive pericarditis made the condition incompatible with life.

Another similarity to the formation of the heart in Eakins and Abbott's case number one lies in the presence of a cardiac aneurysm. Such aneurysm deserves particular consideration: Is its floor the result of normal progression in the formation of the interventricular septum, irrespective of the obstacle to the course of the blood from the right to the left side of the heart which it represents? Or is it the result of an endocarditis which, during fetal or extrauterine life, sealed a previously fairly beneficial arteriovenous shunt through the incomplete interventricular septum? We cannot decide this question.

SUMMARY

1. A 65-year-old woman with heart disease, who had begun to have congestive heart failure in Feb., 1933, required repeated hospitalization because of congestive failure until her death four years later. The essential findings in the heart at her last admission were a loud systolic murmur best heard at the second and third left intercostal spaces, accompanied by a thrill, and followed by a moderately loud aortic diastolic murmur. There was no unusual amount of cyanosis and no clubbing of the fingers or toes. The diagnosis was rendered difficult by the history of rheumatic fever, the moderate hypertension, and the positive Hinton and Kahn reactions, as well as the fact that she was at the age when arteriosclerosis could be a prominent factor. She was finally thought to have congenital heart disease, probably with an interventricular septal defect, and syphilitic aortic regurgitation. It must be mentioned that calcareous aortic stenosis was strongly considered, but was second choice.

2. A partial autopsy showed an incomplete, fibromuscular, *intra*-ventricular septum at the junction of the pulmonary conus and the body of the right ventricle (pulmonary conus stenosis). The *inter*-

ventricular septum was complete, but was covered with thickened endocardium in the form of a small aneurysm. All the fetal passages were closed. The free edges of the intraventricular septum, as well as the pulmonary, tricuspid, and mitral valves, were free from secondary disease. The aortic valve showed a calcareous stenosis. There was acute adhesive pericarditis.

3. The anomaly of the right side of the heart is considered as a congenital malformation consisting of arrest of the process of separation between the pulmonary conus and the body of the right ventricle with subsequent complete closure of the interventricular septum. The manner and time of the closure of the interventricular septum are not determined. Possible causes of an aneurysm in the interventricular septum and its effects upon the circulation are mentioned.

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TRUE COR BILOCULARE IN IDENTICAL TWINS

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TRUE cor biloculare is a grave anomaly of rare occurrence. Some fourteen cases have been reported, nine of which were analyzed by Maude E. Abbott. In nine of the fourteen cases cor biloculare was the primary lesion, but in five instances this lesion complicated other defects. The most commonly associated anomaly was one of the vessels, usually a persistent truncus.

REPORT OF CASES

Baby boy F ("A"), who weighed 2280 gm. and was 46 cm. in length, was delivered by breech extraction. Baby boy F ("B"), who weighed 2820 gm., was 52 cm. in length and was delivered spontaneously and normally.

Two placentas were expressed, connected by membranes. The septum between them was thick and could not be separated. The membranes could be separated easily. There was no connection between the circulations of the placentas. There were no cord anomalies.

The mother had had two previous pregnancies, both uneventful. One child is 3 years of age, the other 11 months of age, and both are well. There was no history of rheumatism, tuberculosis, or heart disease; neither was there a history of any infectious disease at the time of delivery. The mother's blood Wassermann reaction was negative. Her stay in the hospital was uncomplicated by illness.

The physical condition of the twins at birth seemed good. They both cried well and their color was good. However, because baby "A" was underweight, he required special treatment as a premature infant.

A complete physical examination was delayed until approximately ten hours after birth. Baby "A," the smaller and weaker of the two, had a systolic murmur which was heard over the entire precordium. No definite cardiac enlargement could be made out. About thirty hours after delivery, this smaller baby suddenly became cyanotic and dyspneic. The heart sounds were feeble; a systolic murmur was still heard over the entire precordium. The child lived only about five minutes after the cyanosis and dyspnea were first noticed. At autopsy, the heart measured 5 by 3.5 by 2.5 cm. and weighed 18 gm. It consisted of one auricle and one ventricle, separated by a tricuspid valve. Both chambers were dilated. The ventricle led into a large vessel, at the beginning of which was a tricuspid valve. This vessel gave off two pulmonary arteries and then formed a normal aorta with normal branches. The lungs presented many atelectatic areas.

At about the same time that baby "A" died, baby "B" developed an ashen cyanosis and dyspnea. However, his heart sounds appeared to be good and no murmurs were heard. A roentgenogram was taken immediately and revealed an enlarged heart, globular in shape. There was a progressive increase in dyspnea and cyanosis, but still no cardiac murmur. This second child died nine hours after his twin brother. At autopsy, the heart was dilated, measuring 4 by 3.5 by 3 cm., and weighed 18 gm. It consisted of only two chambers, one auricle and one ventricle, between which was a tricuspid valve. The ventricle opened into a vessel guarded by a tricuspid semilunar valve. This vessel gave off two pulmonary arteries and then continued as a normal aorta with normal branches. The lungs presented a few atelectatic areas.

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The complete autopsies revealed no other congenital defects or evidence of other disease in either infant.

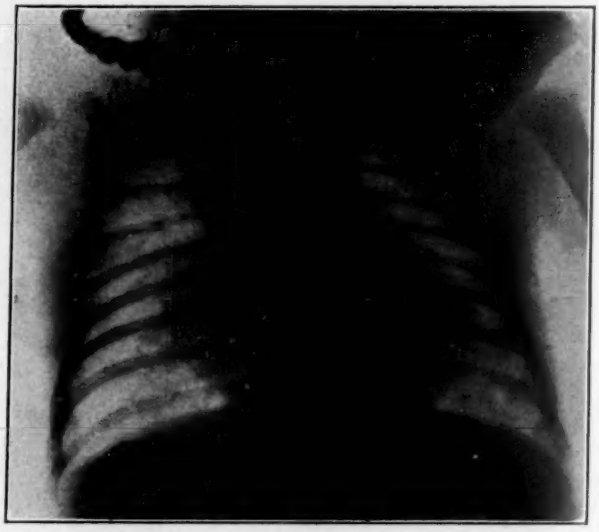

Fig. 1.—Roentgenogram of Baby "B."

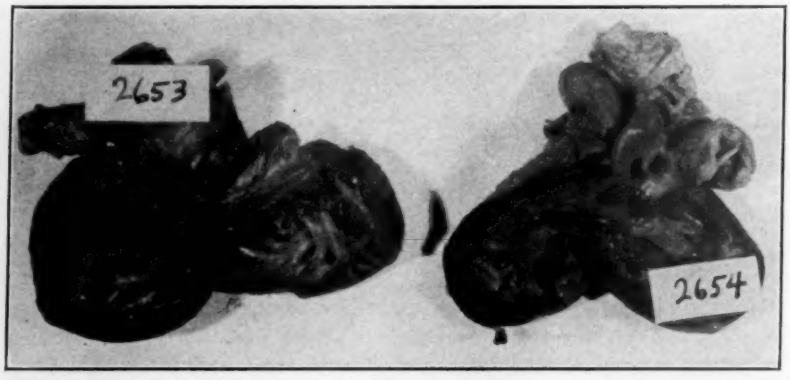

Fig. 2.—Identical double-chambered hearts of the twins. The heart on the left is photographed to show the auricle and ventricle and tricuspid valve, while that on the right is arranged to show the valve and ventricle and the efferent artery in which two pulmonary orifices are visible.

SUMMARY AND CONCLUSIONS

Twin babies who weighed 2280 and 2820 gm. succumbed to identical congenital lesions of the heart and vessels approximately 30 hours and 39 hours, respectively, after birth. The lesion of the heart was true cor biloculare, and the associated anomaly was a persistent truncus.

These cases are reported because our search of the literature has failed to disclose any similar instance in which identical twins suffered from cor biloculare with persistent truncus.

Department of Reviews and Abstracts

Selected Abstracts

Strong, Kenneth C.: A Study of the Structure of the Media of the Distributing Arteries by the Method of Microdissection. Anatomical Record 72: 151, 1938.

Microdissection studies of the arteries of a number of animal species reveal the media to be composed of compact, concentric laminae of obliquely directed, fusiform muscle cells united so closely as to suggest a syncytial character. The cells are organized into a continuous spiral structure.

The functional significance of the organization of the arterial muscle into a continuous spiral structure is discussed. The studies suggest the possibility of distributing arteries contributing to the forward movement of the blood by their intrinsic motor activity.

Illustrations of the continuous spiral structure of arterial muscle are contained in two plates.

Segal, Harry L.: Cigarette Smoking. Am. J. M. Sc. 196: 851, 1938.

Cigarette smoking can be the cause of fatigue in some people and this fatigue can be relieved by stopping cigarette smoking.

Cigarette smoking produces definite changes in the electrocardiogram, mainly: (1) an increase in the heart rate; (2) a lowering of the T-wave.

Both standard and the so-called denicotinized brands produce the same effects.

Although the filter-holders described decrease the amount of nicotine in cigarette smoke, a sufficient amount of nicotine is still available to produce the above changes in the electrocardiogram.

These effects occur mainly in people under 50 years of age.

AUTHOR.

Moia, B.: A Study of the Ventricular Complex in Electrocardiograms With Left Axis Deviation. Rev. argent. de cardiol. 5: 75, 1938.

A total of 338 electrocardiograms showing left axis deviation (deep S_{III}, R_I greater than R_{III}, the entire QRS complex lasting no longer than ten seconds) were analyzed. They were obtained from 316 ambulatory patients submitted to complete cardiovascular studies. They fell into four groups:

1. R_3 small, S_3 deep, 222 records (60.22 per cent). In 102 there was no S_2 wave; of these 13.72 per cent had S-T changes in all leads (low in 182, high in 3) and 11.76 per cent had negative T_1. There was no clinical evidence of heart disease in 17.69 per cent.

In 122, S_2 waves were marked; of these 13.10 per cent had S-T changes as noted above and 11.40 per cent negative T_1. There was no clinical evidence of heart disease in 8.83 per cent.

2. S_3 preceded and followed by small positive peaks (triphasic QRS), 64 cases (18.93 per cent). Of these 6.50 per cent had S-T changes, and as many had inverted T_1 waves. In 18.7 per cent no evidence of heart disease was shown.

3. Deep Q_3 with or without subsequent S-wave. Twenty-eight records, or 8.28 per cent of these, 21.43 per cent had marked S-T changes, and 14 per cent negative T_1. Of these, 25 per cent had no evidence of clinical heart disease.

4. M- or W-shaped QRS_3, 22 records (6.50 per cent). None of these showed changes of the S-T segment or T-wave changes. No evidence of heart disease was shown in 22.78 per cent.

All of the patients without demonstrable heart lesions had involved T_2 waves, except one patient in Group 1*B* and two in Group 3. With left axis deviation, therefore, an upright T_2 is almost certainly pathologic. Also in borderline cases there was a marked tendency for T_3 to be inverted.

Changes in the S-T segment (lowered in Leads I and II, elevated in Lead III) and inverted T-waves in Leads I and II, are almost certainly pathologic in cases of left axis deviation.

In left axis deviation an S_2 with a low N_2 or a low R_2, whether it is notched or sharp, usually indicates severe myocardial damage though not always coronary disease.

JENSEN.

Russafiea, Adriana, and Puddu, Vittorio: The Action of Digitalis on the Precordial Lead of the Electrocardiogram. Cuore e circolaz. 22: 453, 1938.

A total of 24 cases (21 normal and 3 cardiac) free from digitalis for at least three weeks were given 0.5 gm. of digitalis daily for four to six days. The chest leads were taken with the technique accepted by the American Heart Association. Most commonly the digitalis was followed by complete inversion of the T-waves, sometimes without corresponding change in the standard leads. In some cases the S-T segment was changed so as to simulate the precordial lead of infarction of the posterior wall; none in this series simulated infarction of the anterior wall.

JENSEN.

Hartog, H. A.: Bundle Branch Block With Short P-R Interval in Electrocardiogram From People With Organic Heart Disease. Nederl. tijdschr. v. geneesk. 82: 5112, 1938.

In a series of four cases of bundle branch block and short P-R interval, the lesion is explained by accelerated A-V conduction rather than by block. One case had also mitral stenosis. There is excellent reproduction of the four electrocardiograms.

JENSEN.

Martin, S. J., and Gorham, L. W.: Cardiac Pain. Arch. Int. Med. 62: 840, 1938.

An attempt has been made to determine the role of the mechanical factor in the initiation of cardiac pain in dogs recovering from anesthesia. It has been found that a typical pain in response can be elicited when tridirectional tension in one plane is applied to a coronary vessel in such a manner as to cause no change in blood flow. With this procedure the chemical factors caused by impaired coronary blood flow are completely eliminated, as shown by the absence of changes in the electrocardiogram. The minimal threshold of tension on ligatures in the coronary vessel was 3 gm. in the series of dogs used. Local application of alcohol can block stimuli initiating cardiac pain, whether mechanical or chemical in origin. It is concluded that tension alone on the coronary arteries in dogs may serve as an adequate stimulus for the initiation of cardiac pain.

AUTHORS.

Heim de Balsac, R.: Parietal Aneurysm of the Heart. Leçons de Cardiologie faites a l'hôpital Brousseis 2: 185, 1938.

This is a fine summary of the subject comparable to that by Parkinson, Bedford, and Thomson in London. It is well illustrated both with pictures and case reports. In almost all cases the aneurysm results from myomalacia following coro-

nary occlusion, though the history of this is often vague. Only 2 to 5 per cent are on a syphilitic basis (gumma). Two-thirds of the patients are men between the ages of 40 and 60 years. Usually the descending branch of the left coronary is affected. The left ventricle is almost exclusively affected. Some aneurysms cause thinning of the cardiac wall only, without change in the external contour of the heart. Such a case is illustrated with contrast medium placed post mortem in the ventricle. The mechanics of the area is shown in a preparation with infected cardiac vessels. Cardiac aneurysms may be multiple. Physical signs are variable and unreliable; the more important ones are discussed in detail. Until the days of systemic fluoroscopy the diagnosis was rarely made during life. Also the electrocardiographic findings are mostly those of various forms of myocardial damage. Many aneurysms can be seen deforming the left border, either as hemispherical prominences or rendering the outline of the rectangular shadow. When paradoxical pulsation is discovered it is an important sign; it tends to disappear later in the course of the disease. In late cases the movements follow these of the ventricular wall but are somewhat delayed, "postsystolic."

Cardiac aneurysms rarely rupture; this accident usually occurs in the acute stages of occlusion. The aneurysm seems to form in the course of three to six weeks. In itself, it has a good prognosis really constituting a form of healing after occlusion, but it is so often associated with serious coronary diseases that the prognosis is determined by this factor.

Taken together, the English and this French paper admirably cover the subject. Both are accompanied by extensive bibliographies which curiously seem to be drawn from widely different sources.

JENSEN.

Puddu, Vittorio: Clinical and Electrocardiographic Observations on 30 Cases of Infarction of the Myocardium. Minerva Med. 2: 9, 1938.

This is a nice study of thirty cases of chief interest to readers not familiar with the condition and to those collecting series for mass analysis. It is well arranged and has illustrations of considerable didactic interest. Twenty cases were diagnosed during life, two at autopsy, twenty-eight were males and two were females. The youngest was 31 years of age, the oldest, 74 years. Six had syphilis. Special attention is given to prodromal symptoms and symptomatic cases. The value of precordial leads is demonstrated. Of eight cases observed in the attack, two died. Of thirty references to the literature, twenty-two are from American sources.

JENSEN.

Gorham, L. W., and Martin, S. J.: Coronary Occlusion With and Without Pain. Arch. Int. Med. 62: 821, 1938.

A study of the clinical histories and necropsy data for 100 patients with proved coronary occlusion showed that 58 had cardiac pain and 42 did not, indicating a higher frequency of painless occlusion than is generally recognized.

The following broad statement may be made regarding Group 1, comprising 58 patients who suffered from cardiac pain in a fatal attack: The patients tend to be younger; males show the peak mortality ten years earlier than do females; a history of preceding attacks of anginal pain and of hypertension is more common; pain overshadows dyspnea as a symptom, and a pericardial friction rub is much more often heard. Actual thrombosis, acute infarction, acute pericarditis, and milder grades of coronary sclerosis are more frequently encountered than in the patients in Group 2. The location of the infarct and the rupture of the ventricle, with resulting hemopericardium, bear no relation to pain.

The following general statement may be made regarding Group 2, comprising 42 patients who had no pain in a fatal attack of coronary occlusion: The patients tend to be older than those in Group 1; the peak mortality is shown to be a decade earlier than in females; a history of preceding attacks of anginal pain and of hypertension is less common; dyspnea is generally an outstanding symptom, and a pericardial friction rub is rarely heard. Old infarcts, with absence of actual thrombosis and pericarditis, are more frequent. Marked sclerosis of the coronary arteries is slightly, though not significantly, more often encountered. The location of the infarct and the rupture of the ventricular wall, with resulting hemopericardium, bear no direct relation to the absence of pain.

A combination of actual thrombosis of the coronary artery and acute infarction was accompanied by pain in every one of the 15 instances in which these two factors were present. A combination of fibrotic narrowing of a coronary artery, without actual thrombosis, plus old infarction and absence of pericarditis, was not accompanied by pain in 12 of 17 patients (70 per cent). All the 5 patients who did have pain suffered only from a slight degree of it; dyspnea was the dominant symptom in 4 of these cases.

The old mechanical theory of cardiac pain advocated by Allbutt and Wenckebach and more recently advocated by Herrmann, which has been generally discarded in favor of Lewis' theory of ischemia, has been re-examined in the light of our study, and the role of a tension in coronary occlusion varies directly with the speed with which increased tension is produced on the wall of the coronary artery proximal to the obstruction and with the pathologic changes in the wall, whether these changes are due to a reduced elasticity or an actual degeneration of the sensory nerves.

The tension factor seems to offer a reasonable explanation, not only for the presence, but for the absence of pain in cases of coronary occlusion.

Added support for the importance of the factor of tension in the production of cardiac pain has been obtained by an experimental study on animals, the results of which are recorded in a separate communication.

AUTHORS.

Brill, I. C.: Coronary Artery Disease and Angina Pectoris; The Present Status With a Review of Some of the Recent Literature. Ann. Int. Med. 12: 365, 1938.

The author has condensed into a single paper a readable summary of the accumulated information upon this vital and increasingly important subject.

McCULLOCH.

Routier, D., and Heim de Balsac, R.: Six Clinical Observations on Congenital Cardiac Malformation of the Type Called "Communication Interauricular." Bull. Soc. belge de Cardiologie, January, 1938.

A study based on the observation of six cases of this anomaly; all were females; two were cyanosed, a fact attributed to some concomitant lesion; symptoms were slight.

Auscultation: A diastolic murmur can be heard over the second arch on the left border, often also a systolic murmur, but without the peripheral signs of the aortic lesion. The diastolic murmur is probably produced by eddies in the dilated pulmonary artery.

X-rays: Marked prominence of the second arch; marked ventricular mass with apex rounded but not submerged below the dome of the diaphragm. Prominent right border; aortic arch hardly visible.

Electrocardiogram: Right axis deviation and marked notching of QRS.

These cases differ from ones of persistent ductus arteriosus by the prominence of the right border and the smallness of the aortic arch.

JENSEN.

Coburn, Alvin F., and Pauli, Ruth H.: A Precipitinogen in the Serum Prior to the Onset of Acute Rheumatism. J. Exper. Med. 69: 143, 1939.

A precipitin reaction occurs between sera taken just before and shortly after the onset of acute rheumatism. It is clear that the reaction is distinct from the precipitation of pneumococcus C substance and of certain of the streptococcus antigens. It is, of course, possible that the phenomenon observed does not represent an antigen-antibody reaction.

Whatever its nature may prove to be, as a working hypothesis this precipitinogen may be considered either a primary or secondary antigen. Its absence in sera taken during phase I and its late appearance in phase II would seem to be against its direct bacterial origin, although this cannot be excluded. Another possibility is a secondary antigen such as the precipitinogen described by Hughes in yellow fever. It has been shown that in rheumatic subjects who develop acute rheumatism, the appearance of circulating antibodies to hemolytic streptococcus is characteristically late. During this delay streptococcal products are presumably free to react with human tissue constituents. Such an interaction might result in the precipitinogen with which we are dealing.

AUTHORS.

Leverton, W. R.: The Heart in Pulmonary Tuberculosis; Electrocardiographic Consideration. Ann. Int. Med. 12: 285, 1938.

A study was made of 416 cases of active pulmonary tuberculosis and 44 inactive cases. The cases were classified according to anatomic position of the heart; 47 showed shift of the heart to the right, 119 to the left, and 250 no shift of heart.

Arterial hypertension was found in 38 of the active cases, but not in any of the inactive cases.

One hundred and eighty-nine, or 45.5 per cent, of the total number of active cases studied showed significant changes in the QRS complex, the RST segment, or the T-wave. None of the inactive cases showed any important abnormality of the electrocardiogram.

There were 19 graphic records which showed an abnormal Q-wave; 12 of these were of the Q_3 type described by Pardee. Thirty cases showed intraventricular block, 43 abnormality of the RST segment, and 119 abnormal T-waves.

The electrical axis is apparently influenced by the rotation of the heart on its longitudinal axis.

The percentage of cases showing an increase in the duration of the QRS depression and elevation of the RST with T-wave changes is higher than expected and suggests that the nutritional disturbance of the myocardium found in pulmonary tuberculosis of long standing may produce an electrocardiographic picture similar to that found in coronary disease.

The electrocardiogram is of value in the diagnosis of cardiac lesions associated with pulmonary tuberculosis. It is frequently the only positive evidence of myocardial disturbance.

AUTHOR.

Ayman, David, and Goldshine, Archie D.: Cold as a Standard Stimulus of Blood Pressure. New England J. Med. 219: 650, 1938.

The literature describing the use of the cold-pressor test of Hines and Brown is critically reviewed. No study was found that had repeated the same technique as that of Hines and Brown in a group of patients with essential hypertension. The test, using the exact technique of Hines and Brown, was repeated in forty-eight subjects with normal blood pressure and eighty-eight subjects with essential hypertension. The results were in close agreement with those of Hines and Brown.

The final significance of the excessive reactions in certain people with normal blood pressure will be known only after these subjects have been followed for a number of years in order to note how many develop true essential hypertension. For the present, the value of the cold test appears to lie in the field of investigation rather than in that of practical application. It is possible, however, that it will eventually prove of real value in general practice to pick out many future candidates for essential hypertension or hypertension during pregnancy or those with past hypertension.

NAIDE.

Rothstadt, L. E.: The Effect of Auricular Fibrillation on the Course of Hypertension. M. J. Australia 1: 813, 1938.

The frequency of auricular fibrillation in 1,000 cases of hypertension uncomplicated by mitral stenosis was 7.3 per cent.

Hypertension uncomplicated by mitral stenosis was present in 49 (or 11.2 per cent) of 435 cases of auricular fibrillation.

Hypertension uncomplicated by mitral stenosis was present in 32 (or 33.7 per cent) of 95 patients who had had paroxysms of auricular fibrillation.

A study was made of 50 patients with hypertension and established auricular fibrillation. All were between 45 and 75 years of age. Auricular fibrillation is commoner in older than in younger patients with hypertension.

The radiologic appearances are described and the difficulties in interpretation are discussed.

Congestive heart failure and embolism were common sequelae.

The response to treatment was variable. Eighty per cent of the deaths occurred within two years of the onset of fibrillation; but with treatment a patient might live for several years.

Post-mortem appearances in seven patients are described.

Thirty-six patients with hypertension and paroxysmal auricular fibrillation were studied.

The prognosis in hypertension with paroxysmal fibrillation is better than in hypertension with established fibrillation, other things being equal.

Quinidine therapy often reduces the frequency of, or abolishes, the paroxysms.

AUTHOR.

Kunkel, Paul, and Stead, Eugene A., Jr.: Blood Flow and Vasomotor Reactions in the Foot in Health, in Arteriosclerosis, and in Thromboangiitis Obliterans. J. Clin. Investigation 17: 715, 1938.

Measurements of the blood flow in the foot in health, in arteriosclerosis, and in thromboangiitis obliterans were made under standard conditions by the plethysmographic method. The flow was recorded as cubic centimeters of blood per minute per 100 c.c. of tissue.

The blood flow to the foot reached a constant level after thirty minutes at 43° C. The flow at this temperature has been designated as the "maximal" flow.

The average maximal blood flow to the foot in normal persons was 17.1 c.c., with the highest 25.9 and the lowest 11.1 c.c. Ninety per cent of the flows were

between 13 and 20 c.c. The average difference in the maximal flow in the right and the left foot was 1.8 c.c.

The maximal blood flow in the foot showed no appreciable decrease with age (17 to 67 years) in the presence of normal cardiovascular system.

The average maximal blood flow in the hand per equal volume of tissue was twice that in the foot. When calculated in relation to skin area the maximal flow in the hand was 30 per cent greater than that in the foot.

The vasomotor reactions of the hand and foot were qualitatively similar. The rhythmic respiratory waves observed during normal breathing resulted from the changes in venous pressure associated with respiration and were not of vasomotor origin. A deep inspiration, however, induced constriction of vasomotor origin in both the hand and the foot.

In arteriosclerosis and thromboangiitis obliterans the maximal blood flow to the foot was reduced 50 per cent without symptoms or trophic disturbances. When the flow was reduced to one-third the normal value, or to the level of 5 c.c. or below, symptoms or trophic disturbances usually occurred.

In both arteriosclerosis and thromboangiitis obliterans severe intermittent claudication in the calf was in some cases incapacitating, though the blood flow in the foot was as great as in many normal individuals. Thus the presence of an adequate supply of blood to the foot did not eliminate the possibility of obliterative disease involving the vessels of the calf muscles.

AUTHORS.

Thomas, K. Jefferson, Cohen, Mandel E., and Hamilton, Burton E.: Studies on the Circulation in Pregnancy. Am. J. M. Sc. 196: 819, 1938.

Lead V of the electrocardiogram was determined 398 times on 288 pregnant women.

The T-wave was observed to be upright in 7.7 per cent of normal pregnant women.

Changes in the chest lead during pregnancy, particularly those in the T-wave, were thought to be associated with changes in the position of the heart.

Lead V is of no particular value in diagnosis of heart disease during pregnancy.

Recognition of normal variation in Lead V of the electrocardiogram during pregnancy will avoid erroneous diagnoses of myocardial disease in pregnant women with normal hearts.

These conclusions apply only to chest leads taken with the electrodes placed in the manner described above (i.e., exploring electrode in the fourth interspace 5 cm. to the left of the sternum, indifferent electrode on left leg) and do not apply necessarily to chest leads taken with the exploring electrode at the apex of the heart.

AUTHORS.

Routier, D., and Heim de Balsac, R.: Modification of the Trachea and Bronchi in Mitral Disease. Arch. d. mal. du coeur. 30: 861, 1937.

By injecting a small amount of lipiodol, the authors brought into clear relief the larger bronchi and showed how enlargement of the left auricle changed their course; first the angle between the bronchi is widened and the left bronchus tends to wind a more horizontal course. Then their course becomes curved to embrace the enlarged auricle "like the legs of a rider gripping the horse." Enlargement of the right auricle does not affect the bronchi, but in cases of large pulmonary arteries, the bronchi may become compressed and the angle between them may become lessened from pressure by these vessels.

JENSEN.

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